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THE REGULATION OF HUNGER AND APPETITE*

Conference Chairman and Consulting Editor

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INTRODUCTION

By Franklin Hollander
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Conferences on hunger and appetite, such as that on which this monograph is based, have been held before, as in the case of the *Nutrition Symposium* at the Harvard School of Public Health in October 1952; but the prime objective has always been to resolve the broad question, "Why do some people get very fat and some very lean?" rather than the more restricted one, "Why do we eat, or fail to eat, even in spite of nutritional requirements?" The papers in this monograph delve into this more delimited area of physiology concerned with the regulation of eating behavior

cern us at all Rather, we shall deal, in these papers, with neural, humoral, and gastrointestinal processes which initiate or inhibit these other muscular activities In analyzing these diverse factors, we shall use a variety of terms Sometimes we shall speak of "the desire or urge or drive to eat" Sometimes we shall talk of "eating for calories, or carbohydrate, or salt, or some other particular entity, because of a special craving for it" Sometimes the phrase used will be "eating for bulk" or an analogous expression We may even have

forms, it was chosen for the title of this monograph Our predecessors in this

operational purposes, or else that they will be discarded from our technical terminology The frequent use of these words in describing human experiences not directly related to the ingestion of food may make the latter the more desirable

Part I. Regulatory Mechanisms

UNTOWARD REACTIONS TO WEIGHT REDUCTION AMONG CERTAIN OBESE PERSONS

By Albert J. Stunkard

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The ill-effects of obesity are so well advertised these days that weight reduction regimens are rapidly achieving the status of panaceas. It is well to be aware that such regimens are not cure-alls, and that they can be more dangerous than the condition they seek to correct.

The emotional disturbances attendant upon semistarvation have been carefully studied in a nonobese group in the Minnesota project.[1] Similar respect has yet to be accorded the overweight patients for whom semistarvation is prescribed with such impunity. Physicians who have dealt with obese patients have noted widely varying responses to weight loss, from the patient who has never felt better, to the one who becomes so weak he can hardly keep going. Furthermore, anorexia nervosa is reported as beginning characteristically during a reducing regimen. Only two publications, however, have published articles directly addressed to the topic of untoward responses to weight reduction. The first article, by Hertz and Means,[2] deals with the precipitation of thyrotoxicosis by weight loss arising either from voluntary restriction of food intake, or from debilitating illness. More recently Bruch[3] has called attention [illegible] precipitated by attempts at weight reduction.

[illegible] rmed [illegible] was [illegible]

[illegible] severity occurred during the entire nondieting experience of the 25 patients [illegible] relations [illegible] ortance in [illegible], only one [illegible] her excess [illegible]

[illegible] ed sample, [illegible] ation as a whole. The illnesses described here, however, constituted discrete reaction patterns, different from the patient's usual adjustment. These reactions were similar enough to warrant a description of some of the common features. The predominant symptomatology was depressive, although anxiety symptoms were present in most of the patients. The first symptoms were those of weakness and fatigue, which were often dismissed by the patient as an understandable feature of the lowered caloric intake. There followed depression of mood with crying spells and sleep disturbance. More severe depressive symptoms,

such as retardation, agitation, and thinking disorder occurred more rarely, but all of the patients experienced such incapacity as to interfere to some degree with performance of their daily activities

An important part of the classical depressive reaction is the self-condemnation held to derive from the miscarriage of mechanisms of hostility and guilt It is therefore significant that such attitudes were not found in any of the nine patients in the course of their "dieting depressions" Instead, the predominant feeling state was one of futility and hopelessness. Furthermore, a general preoccupation with deprivation was often generalized from concern with food to interpersonal issues Finally, half the patients manifested habit deterioration with decreased concern over personal hygiene.

An attempt was made to determine those characteristics which might help predict which patients would react thus unfavorably to weight reduction programs The psychiatric diagnostic type was of little value Although this group contained a high incidence of persons with personality disorders, those falling ill represented a variety of diagnoses including schizophrenic adjustment, depressive character, and obsessional character During the reducing regimen, precipitating events were either not apparent or not common to the group. Thus, neither the duration of the weight reduction program nor the amount of weight lost seemed significant

The one feature which was common to all the patients who became acutely disturbed was the presence of the "night-eating syndrome" This syndrome has been described[4] as a pattern composed of evening hyperphagia, insomnia, and morning anorexia Its incidence appears to be confined to individuals with a problem in regulation of food intake It is accentuated during periods of emotional disturbance and is considered to represent a response to stress of a type peculiar to certain obese patients Attempts at weight reduction in the presence of the night-eating syndrome have been remarkably unsuccessful Few patients manifesting the syndrome were able to maintain a reducing regimen long enough to lose an appreciable amount of weight When they did, one of the emotional disturbances described above usually followed

Further study is needed to define more clearly the nature of these illnesses, which appear to be neither schizophrenic reactions nor true depressions Nevertheless, enough is already known to require that careful and continuing attention be paid to the emotional state of any patient who is placed on a reducing regimen

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THE ROLE OF THE DIGESTIVE TRACT IN REGULATING THE INGESTION OF FOOD

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The most important *basic* driving forces or urges that regulate the activities of human beings and animals are (1) hunger for food, (2) hunger for salt, (3) thirst, (4) sexual drive, and (5) the desire for the preservation of life. Thus, we are well justified in attempting to understand one of these basic forces and

*presented which indicates that regulation of food ingestion results from an inte*gration of forces derived from special movements of the digestive tract, hormone influences, emotions, impulses from the cerebral cortex, from the hypothalamus, and perhaps from the entire body.

In considering the over-all regulation of food ingestion, the terms hunger, appetite, anorexia, *etc.* have been extensively employed. These terms have different meanings to various students of this subject. We shall accomplish much if we agree on our basic terminology, if we approach the subject cautiously, avoid broad generalizations, and carefully attempt to justify our transference of observations and interpretations from the species studied to other species.

It has frequently been stated that the intake of food is rather accurately

rate correlation of food ingestion and food requirement is ascribed to an automatic increase or decrease in the desire for food as the need for food increases or decreases It is common knowledge that a growing child, a convalescent individual, a person performing heavy manual labor, or a pregnant woman all require relatively more food, and that an increased desire for food automatically tends to parallel the need Admitting that this parallelism usually exists, it

non and Washburne[1] have demonstrated, were produced by special movements called "hunger contractions" of the stomach. These movements and the sensations they produce have been extensively studied by Carlson[2,3] and his associates Serious consideration of these hunger contractions is thoroughly justified. It has repeatedly been demonstrated that they provide one of the

iat are carried by

atory and cardiac

are appreciated.

These sensations, like most visceral sensations, are poorly defined and difficult to describe. They produce a feeling of emptiness, a disagreeable or painful sensation of tension, or a "hunger pang" localized in the epigastrium. Usually, these epigastric sensations are associated with increased nervous excitability, restlessness and, sometimes, weakness, headache, lassitude, and nausea. An outstanding feature of the hunger contractions and hunger sensations is their periodicity.

In the normal adult, 24 hours postprandial, periods of hunger contractions usually occur at one to one-and-one-half-hour intervals. The activity consists of peristaltic waves that usually begin near the cardia and may even involve the lower esophagus. These waves progress over the entire stomach, finally involve the duodenum, and then die out. They usually pass over the stomach at 20-second intervals, and the period of activity persists for approximately 30 minutes. During the latter portion of the active period, the gastric tonus becomes greater, and the epigastric distress is more acute.

It has been conclusively demonstrated that hunger contractions are real and occur spontaneously in man and animals, for they have been (1) seen by Carlson in an individual with a gastrostomy, (2) felt by the hand placed on the abdominal wall; (3) seen as ripples of the abdominal wall of individuals with diastasis of the recti, (4) recorded by Templeton and Johnson[4] from an open tube introduced into the proximal end of the stomach, (5) seen fluoroscopically, following the swallowing of a mouthful of barium sulfate in the outliner technique, (6) recorded by Gianturco[5] from radio-opaque clips fastened to the gastric serosa to outline the stomach, and (7) recorded, chiefly by the balloon-water manometer technique, which probably exaggerates the movements.

The hunger contractions occur as a peristaltic wave which usually involves, in sequence, (1) the gastric fundus, (2) the corpus, (3) the antrum, and (4) the proximal duodenum. Weak waves may originate in the midstomach and progress to the distal antrum and the duodenum without involving the gastric fundus. A hunger wave of moderate intensity passes from the proximal to the distal end of the stomach in one to two minutes. When the waves are exaggerated, they develop more frequently, progress more rapidly, and are of greater magnitude, and the gastric tonus is augmented. During vigorous activity, several waves may be progressing over the stomach simultaneously. The peristaltic nature of hunger contractions has been intensively studied by Rogers and Martin,[6] Templeton and Johnson,[4] Quigley, Johnson, and Solomon,[7] Quigley and Solomon,[8] and by Meschan and Quigley.[9]

With longer fasting, the periods of gastrointestinal activity become more prolonged, the periods of rest are shortened, and the activity is nearly continuous. The tonus of the digestive tract is gradually increased, so that the stomach and adjacent portions of the gut remain partially contracted for long periods. Parallel with this augmented tone and motility, the hunger sensations become more severe and more continuous.

This distress tends to become so acute as to produce a very intense desire for food. If ordinary food is not available, the subject may feel compelled to eat many distasteful substances. Reports are numerous of individuals who

ere driven by hunger to eat worms, grubs, grass, and the roots and bark of trees. The veneer of civilization may be sloughed off and hungry men will lie, steal, or commit murder or even cannibalism to obtain relief from distress caused by lack of food. The story of the Donner Party of settlers from Illinois illustrates the situation. This group, while on their way to California in 1846, became snowbound in the Sierra Nevada Mountains. When their supply of food became exhausted, they killed and ate their cattle, oxen, horses, dogs (including the entrails, horns, and hoofs of the animals). The harnesses, belts, shoes, and finally members of the party and members of their own families were eaten in an attempt to relieve the hunger distress. The reactions of human beings to starvation have been thoroughly described by Ancel Keys in *The Biology of Human Starvation*.[10] Under the influence of hunger, animals will attempt many desperate acts. They will attack other animals or humans whom they ordinarily fear, and normally timid, wary animals, such as the deer and elk, will approach human habitations in search of food. It has repeatedly been demonstrated that hunger can be very distressing and can profoundly influence human and animal behavior.

The sensation of hunger is not frequently experienced by normal adult civilized men eating three meals each day, but it readily develops during voluntary or involuntary starvation, with persons on a hunger strike, with mariners adrift in inadequately provisioned life boats or rafts, or with castaways in uninhabited country. Hunger contractions begin in infants or puppies shortly after a meal is evacuated from the stomach. Apparently, these contractions produce disagreeable sensations for, while they are present, the newborn becomes restless, puts various objects into its mouth to test their suitability as food, and frequently cries. An outstanding characteristic of hunger is its relief by the ingestion of food.

On the basis of the relief from hunger distress that follows the ingestion of food, the young individual develops the *conditioned reflex* of *appetite*. Hunger, in a restricted sense, consists of the various disagreeable sensations associated with the inadequate intake of food. Prominent components of these disagreeable sensations are the sensations produced by the hunger contractions. Hunger is a primitive, unconditioned mechanism which tends to induce this individual to ingest food. Appetite is founded on the learning or memory of (1) the disappearance of the hunger sensations and (2) their replacement by the pleasurable sensations associated with the comfortably filled stomach, of satiety, well-being, relaxation, and drowsiness. Appetite is also related to the agreeable taste, smell, and appearance of food. Appetite becomes so developed in the civilized human adult that it usually constitutes the major force regulating the intake of food. Apparently, the same relation between hunger and appetite applies to well-fed house pets (dogs and cats), poultry, animals in zoos, *etc.*

Civilized men eat at times which are established by habit, because the clock indicates that it is 7 A.M., or noon, or 6 P.M., or because they have heard the noon whistle, or because other persons are *eating*, and similar factors.

The quantity of food ingested at one time can be influenced by both hunger and appetite. A starved, *i.e.*, a hungry, person tends to gorge himself when

food becomes available Appetite may induce a person who has reache satiety from meat, bread, and vegetables to eat an appealing dessert.

Since appetite and hunger usually lead to the ingestion of food and, since they are closely interrelated in development, it is frequently difficult to ascertain, on specific occasions, whether food is being eaten by man or animals because of hunger or appetite It is helpful to relate *hunger* to the *disagreeable sensations* and *appetite* with the *pleasant sensations* which influence the ingestion of food Our studies of hunger become more specific if the hunger sensations are related to the objective information obtained from records of hunger contractions

It is not essential that animals or humans experience sensations from the contracting empty stomach to have a desire to ingest food We have observed, and so have many others, that food intake is not significantly decreased in dogs or man by cutting both vagi, cutting the splanchnics, by vagotomy combined with splanchnectomy and celiac-ganglionectomy, or by partial or total gastrectomy Decorticated dogs or anencephalic infants will not seek food but will swallow what is placed in their mouths Such observations should not be interpreted as evidence that hunger contractions play no role in regulating the ingestion of food Food intake is an activity so essential to the maintenance of health and life that nature has provided several mechanisms which influence it These mechanisms insure that food will be ingested reasonably well even in the absence of sensations from the contracting stomach or from taste or smell receptors

I am most familiar with the studies my associates and I have made on hunger sensations and hunger contractions Therefore, in this presentation, I plan to emphasize chiefly the relation of hunger contractions to the sensations of hunger, especially as indicated by our studies on this subject I am thoroughly aware of the fact that others have conducted investigations similar to or identical with ours, and I shall try, when it is feasible, to correlate our observations and interpretations with those of other investigators

Many of the studies on the factors influencing the ingestion of food and, especially, on the investigation of hunger contractions have been made in connection with dogs and other animals The interpretation of the results derived from these animal studies and, especially, their relation to human hunger sensations should be made with caution Detailed comparisons, however, have repeatedly shown that the contractions in the empty stomach of the dog and of other animals, as recorded by standard methods, closely resemble the hunger contractions of man Thus, the contractions of the empty stomach of an animal are commonly designated as hunger contractions Much evidence indicates that this designation is valid, but the assumption apparently is not amenable to positive proof Perhaps studies on the higher apes would indicate more definitely whether we are entirely warranted in assuming a similar relationship between hunger contractions, hunger, and appetite in both animals and man Many studies on the quantity of food ingested by animals and the avidity with which they ingest the food can be directly interpreted in terms of the animal's desire for food From such studies it has been shown, in animals, that the desire for food closely parallels the hunger contractions

The Portion of the Digestive Tract from which Hunger Sensations Originate

From his visual observations made on a subject with a gastrostomy and [illegible]

in the fundic portion of the stomach. He noted that motility in the pyloric antrum, during digestion, when no sensation of hunger was produced, may be as great as that occurring [illegible]

studied gastric motility simultaneously in the fundus, corpus, and antrum, and concluded that sensations of hunger coincided with antral activity.

Quigley, Johnson, and Solomon[7] also employed the triple tandem balloon technic for a detailed study of the hunger sensations. The subject in whom gastric activity was being recorded was unable to see the record When he experienced hunger, he signaled this sensation by closing appropriate keys in circuits containing signal magnets Quigley and his associates concluded from such studies that each peristaltic wave which passed over the stomach produced only one hunger pang, but this sensation could arise from activity in either the fundus, corpus, or antrum Motor activity in the distal stomach was the more common cause of the hunger pang The portion of the stomach from which the sensation arose might vary in an individual during an experiment. There was a lag of about two seconds between the beginning of the contraction which produced a hunger pang and the recognition of the sensation. Similarly, the sensation persisted briefly after the termination of the contraction With [illegible] ight begin in the fundus while the pre- [illegible] *A continuous hunger distress was then* [illegible] to individual contractions in specific portions of the stomach At such times, several peristaltic waves were progressing over the stomach simultaneously. The sensations related to this motility were overwhelming and could completely change a person's temperament and behavior The desire to obtain relief from his distress was predominant and completely dictated his behavior The individual tended to be [illegible]

period, we made records simultaneously from the stomach and from other portions of the digestive tract Quigley and Solomon[8] employed a double tandem balloon in the duodenum, and a triple tandem balloon in the stomach We confirmed the report of Ivy, Vloedman, and Keane[11] that the hunger periods in the stomach and duodenum were related. We observed that peristaltic waves from the stomach usually passed over the pyloric sphincter and continued as peristaltic waves in the proximal duodenum Occasionally, the contractions in the duodenum differed in time and magnitude from those in the stomach, and the subject accurately localized from his sensations the site and type of contractions occurring The period of duodenal activity some-

times preceded the onset of gastric activity by 15 minutes, and was accompanied by an ill-defined but not especially unpleasant sensation of mild hunger localized deep within the abdomen and about 2 cm. cephalad and 3 cm. to the right of the navel The sensations were related to individual duodenal contractions A hunger period in the duodenum frequently terminated in an interval of incomplete tetanus persisting for approximately three minutes The sensation of hunger during this period was distinctly unpleasant. When vigorous contractions were present simultaneously in the stomach and duodenum, the hunger sensations from the stomach predominated over those from the duodenum, and the location of the hunger sensation shifted to the region of the xyphoid cartilage Meschan and Quigley,[9] Brody, Werle, Meschan, and Quigley,[12] and Quigley and Reed[13] also studied the relation between gastric and duodenal motility

As previously indicated, when the motility was moderate, accurate correlation between sensations and discrete contractions obtained When, however, digestive tract motility and *tone* were exaggerated, the hunger sensation was continuous and very uncomfortable, and was associated with a sensation of restlessness and abdominal constriction The subject became weak, irritable, and ill-tempered The subject indicated the continuous sensation of hunger by persistently holding the keys closed When the subject fasted for two to three days, gastric motility and hunger sensations developed which resembled those produced by the administration of insulin after a fasting period of 24 hours.

Many attempts have been made to ascertain the basic factors which regulate hunger contractions and the associated hunger sensations Carlson (1916) summarized the work performed on this subject up to that time by concluding that "The gastric hunger mechanism is primarily automatic or independent of blood changes as well as of central nervous influences, but, in the normal individual, chemical changes of the blood as well as nervous impulses from the brain and spinal cord augment or decrease this primary automatism in a way to correlate it with the needs of the organism "

That the peripheral gastric hunger mechanism is primarily automatic has been substantiated by the observation of comparatively close agreement in the spontaneous motility of the Heidenhain pouch and the main stomach noted by Robins and Boyd,[14] the denervated Heidenhain pouch and the main stomach by Bercovitz,[15] the transplanted completely denervated pouch by Farrell and Ivy,[16] and several completely denervated gastric preparations by Quigley, Zettleman, and Ivy[17] These experiments also suggest the control of gastric hunger contractions by a constituent of the blood It is reasonable to anticipate that nature would provide a mechanism by which hunger contractions and hunger sensations would be dependent on the availability and utilization of a specific food component

Luckhardt and Carlson[18] reported that gastric hunger contractions are augmented in normal dogs by the intravenous injection of blood taken from fasted or diabetic dogs The idea of a modification of the composition of the blood which would normally regulate hunger contractions was put into definite form

by Luckhardt's suggestion that hunger contractions were increased by fasting, moderate exercise, hemorrhage, exposure to cold, phlorhidzin, or diabetes since, in these conditions, there was either a decrease in the blood sugar concentration, in the glycogen reserve, or in the ability of the body to use carbohydrates. This suggestion was supported by the observation of Bulato and *Carlson*[19] *that insulin injected into dogs increased gastric motility.*

We made an extensive comparison[7, 8] in normal individuals of the gastric and duodenal contractions and the hunger sensations occurring spontaneously during fasting and those following the administration of insulin Insulin hypoglycemia produced no type of motility which differed from the spontaneous fasting motility However, the hypoglycemia exaggerated the motor activity, apparently by augmenting the vagal influence on the stomach [20] The gastric tone was increased, the peristaltic waves were more frequent and of greater magnitude, and the motility persisted for long intervals (in excess of five hours) The rest periods which are characteristic of spontaneous hunger contractions were abolished by the hypoglycemia The hunger sensation became exaggerated and continuous during the period of hypoglycemia. An overwhelming desire developed to eat and "fill an empty space in the abdomen " If the subject was allowed to eat, only slight consideration was given to the character of the food eaten

Mild spontaneous hunger contractions may be inhibited by smoking, mild nausea, unpleasant emotions, body discomfort, the sight, thought, or taste of food, or by extraneous disturbances These factors did not abolish the well-developed exaggerated gastric motility induced by insulin hypoglycemia.

Since many studies indicated a close relation between carbohydrate metabolism, *hunger contractions, and hunger sensations, we investigated this subject* more extensively. We found that, as the administration of dextrose, intravenously or into the intestine, relived insulin hypoglycemia, the exaggerated hunger contractions and hunger sensations also disappeared If the quantity of dextrose was moderate, however, the relief of the hypoglycemia was transient With the return of the hypoglycemia, hunger contractions [illegible] again exaggerated

periods of hunger contractions Similar observations and conclusions were obtained by Scott, Scott, and Luckhardt [22]

Quigley and Lindquist[21] produced in dogs several of the conditions which, Luckhardt had postulated, should *exaggerate hunger contractions, i e, hypo*glycemia, glucosuria, and ketonuria for 6 to 15 days by the administration of phlorhizin. Although the true blood sugar decreased from a normal of approximately 80 mg per 100 cc to about 50 mg under the influence of phlorhizin, the hunger contractions were not exaggerated but were depressed during this period, and some anorexia was present As the effects of the drug passed off, the blood-sugar level, the hunger contractions, and the desire for food returned

to normal. This study definitely demonstrated that disturbances in carbohydrate metabolism involving a significant hypoglycemia did not necessarily augment the hunger contractions or the desire for food. Stucky, Rose, and Cowgill[24] also demonstrated that blood-sugar level was not related to hunger contractions or the desire for food in vitamin B-deficient dogs

Quigley and Hallaran[25] apparently obtained conclusive evidence that spontaneous hunger contractions were not basically dependent on the blood-sugar level It had been reported that the intravenous administration of dextrose inhibited spontaneous hunger contractions Quigley and Hallaran demonstrated that a similar inhibition could be produced by the manipulations incident to the intravenous injection of inactive substances such as 0 9 per cent NaCl By employing suitable precautions to minimize such vitiating factors, these investigators demonstrated that 1 to 25 gm. of dextrose could be administered intravenously and the true blood-sugar level maintained above 160 mg for at least an hour without significant modification of the spontaneous hunger contractions Hanson and Grossman[26] also demonstrated that the intravenous administration of 40 to 80 gm of dextrose daily for seven days did not significantly modify the food intake of dogs during that period Quigley and his associates[7, 17, 25, 27, 28, 29] demonstrated that food substances confined to the stomach did not inhibit hunger contractions. On the contrary, the substances might stretch the stomach and augment the hunger contractions However, when glucose, sucrose, lactose, fats, or fat split products entered the upper intestine, the stomach was inhibited Since this inhibition occurred even when the stomach was denervated, it was concluded that an inhibitory substance which differed from that administered was carried by the blood to the gastric musculature We obtained evidence that the gastric inhibitory substance released from the intestine was enterogastrone

Slides

Four slides were exhibited at the conference at which this paper was presented, showing various types of gastric and duodenal motility recorded from fasting men On some occasions, the gastric motility was exaggerated by the administration of insulin The hunger sensations associated with each type of motility were reported

One slide was presented showing the surgical preparation employed to introduce food substances exclusively into either the stomach or the duodenum. Food in the stomach did not inhibit hunger contractions If the stomach were significantly distended, gastric motility was augmented

Two slides were presented showing that the introduction of fat or dextrose into the duodenum inhibited gastroduodenal motility This inhibition probably explains the termination of hunger as the result of feeding

Five slides were presented showing three methods employed in completely denervating the stomach When fats, fatty acids, soaps, dextrose, lactose or amino acids were placed in the intestine, contractions were inhibited even in the denervated stomach, apparently through the action of the inhibitory hormone enterogastrone which was released from the proximal intestine

Summary

Evidence is reviewed demonstrating that, during fasting, augmented states of tonus and motility called hunger contractions occur in the stomach and duodenum This motor activity produces hunger sensations which serve as the basic factor regulating the ingestion of food Appetite develops from the hunger sensations. Apparently, the relation between hunger contractions,

contractions and hunger sensations probably through the intermediation of the hormone enterogastrone

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REGULATION OF ENERGY INTAKE AND THE BODY WEIGHT: THE GLUCOSTATIC THEORY AND THE LIPOSTATIC HYPOTHESIS*

By Jean Mayer

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The Merriam-Webster dictionary defines hunger as (1) a craving for food, and (2) any strong craving Appetite is defined as the natural desire for satisfying some want or need, as of food Other definitions have introduced emphasis on this or that component Carlson,[1] for example, has defined hunger as "a more or less uncomfortable feeling of pressure and pain referred to the region of the stomach", Grossman and Stein,[2] in an excellent article on hunger feelings following insulin and their persistence after vagotomy, have distinguished between the sensation of being "hungry all over" and epigastric pangs Other authors have emphasized differences in psychic associations, as well as in intensity, between appetite and hunger All these considerations should make it clear that hunger and appetite are generally understood to be sensations or feelings that, as such, are not properly amenable to regulation The sensory meaning has been so generally accepted that, desirable though it may be to reject it, as suggested by Doctor Hollander, it seems a little late in the day to do so

It is even difficult to record the appearance of these sensations and, *a fortiori*, their intensity, except through a behavioristic approach As all of us have known empirically since childhood and as can be clearly evidenced in the laboratory, a multiplicity of factors, emotions, urges, environmental temperature, necessity for exercise, will interfere to modify the tendency to partake of food Often, the course of action in time of these factors is complex acute exposure to cold will inhibit tendency to eat in a first phase, yet increase it later When dealing with a problem which can be attacked only behavioristically and which depends on a multiplicity of variables, the only systematic approach that I know of is the statistical method of Skinner, who studied the frequency or probability of responses to this or that stimulus With the collaboration of Anliker, an experimental psychologist versed in the "Skinner box" techniques (as well as in electronics and recording techniques), we have recently embarked on the study of the probability of response to exposure to food and on the frequency of work for food of normal mice, as well as of littermates with the hereditary obese hyperglycemic syndrome, goldthioglucose obesity, and hypothalamic obesity This study will enable us, we hope, to obtain analysis of correlations of response to various physiologic stimuli, as well as an exploration of how much conditioning can be introduced in these responses Results, however, are too preliminary to warrant a report at this date Even then, of course, they will not deal with a regulation, but only with a pattern of feeding

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In man, the wide variations of patterns (*e g* normal-weight individuals and groups, with similar occupations, apparently have successfully habituated themselves to widely different numbers of meals per day, distribution of calories within these meals, *etc*) suggest that it is not the initiation of eating (as a behavioristic translation of hunger or appetite) that is regulated.

The distinction between hunger feelings, hunger states, and hunger behavior introduced by Janowitz and Grossman,[3] although it presents great descriptive interest (we shall see later that, in effect, one way to look at the glucostatic [illegible]

and appetite and examine, instead, the subjects of regulation of food intake and body weight, two measurable quantities related to the stated topics I should also parenthetically deplore the fact that distance interferes with personal discussion of these subjects by two of the investigators who, in my judgment, have made the most important contributions in this field in the last two decades, Professor André Mayer, of Paris, France, and Doctor Gordon C Kennedy, of Cambridge, England.

Let us examine the problems which arise with respect to the following four questions: Is there a regulation? What is regulated? How well is it regulated? and, finally, How may it be regulated? It should be emphasized that, in the discussion which follows, we shall be concerned, not so much with the factors that, at any given time, make for initiation of feeding or even its continuation These factors will be reviewed by Doctor Brobeck with the customary excellence I learned to anticipate when I was his student We shall be concerned essentially with the "memory" of such factors in time, or with those factors which exhibit memory, a necessary attribute for anything which participates in a lasting regulation

I *Four Problems*

(1) Is there a regulation? This question, as André Mayer and his co-workers[4] have shown, is best answered, not by consideration of food intake, but by consideration of the frequency of appearance of values representative of total weight, water content, reserves other than water, nitrogen balance, and fat content[5] Kennedy has presented striking evidence of the persistence of regu- [illegible]

[illegible]

its cells, organs, and systems It simply sets limits both upward and downward to energy exchange, for expenditures, a maximum (the "summit metabolism" of Giaja[9] and a minimum ("basal" and its variations) As regards food intake, the upper limit has since been explored by Kennedy[10] in his beautiful demonstration that, in the rat, lactation, not hypothalamic hyperphagia represents the peak of intake, and that the intake is not further increased by

superimposing the latter on the former, but can be increased by superimposing cold on lactation

If the margin of variation of this "biometric regulation" were small, there would be no need for any additional regulation. In fact, however, the margin is large, thus allowing the animal to adapt to variable environmental conditions

(b) *Adaptation of energy intake to energy output (short-term, generally day-to-day regulation of energy intake)* This regulation appears to be the most important mechanism It adjusts intake to requirement Within the biometric margins, the balance may be reached at various levels, corresponding to reserve (fat) depots of various sizes, depending on circumstances

(c) *Corrections of the errors in (b) (short-term mechanisms of regulations of food intake) by successive recompensations (long-term regulation of reserves, closely related to regulation of body weight)* Such a mechanism functions by successive oscillations around the equilibrium condition or the steady gain characteristics of growth or incipient obesity It corrects the errors of Gasnier and Mayer's regulations,[8] regarding either excessive or deficient intakes It is not a very accurate or sensitive mechanism On the other hand, it is one of extreme importance In fact, from a clinical standpoint, it is the long-term mechanism which is of importance in any attempt to correct the body weight either upward or, more frequently, downward Again, Kennedy[10] has extended Gasnier and Mayer's findings to at least one type of abnormality by demonstrating that, even in hypothalamic obesity, there existed a well-defined, long-term mechanism of food intake and body weight

(3) How well are these regulations functioning? The concepts introduced by Gasnier and A Mayer of characteristic parameters of regulation and their application of these concepts to the short-term and long-term regulations (i.e., precision, day-by-day reproducibility, sensitivity, and rapidity) will be briefly described and numerical examples given

(4) What is the mechanism of these regulations? This part is the only one for which this article can claim any originality The glucostatic mechanism for the short-term regulation of energy intake (which perhaps could be called the physiologic basis for the hunger state and the hunger behavior, if that classification is followed) and the possible working of a lipostatic long-term regulation of food intake and body weight will be mentioned.

II *Existence of Regulations of Food Intake. Short Term Regulation (Adjustment of Energy Intake to Energy Output) Long Term Regulation (Body Reserves and Weight)*

FIGURE 1 illustrates the frequency of day-to-day appearance of value of "reserves" (variations of body constituents other than water) for 23 rabbits[9] The average weight of these rabbits was about 2900 grams These animals were maintained for 80 days at a temperature of 18 to 20° C, in an atmosphere 85 per cent saturated with water vapor Variations of reserves (body constituents other than water) were calculated from careful food and water balance studies It is readily seen that, under these conditions and for that particular group of rabbits, variations of dry weight were small The picture clearly

suggests the existence of regulations Similar pictures were obtained for water and nitrogen balances.

FIGURE 2 gives energy intake as a function of energy output for these 23 rabbits[5] The energy equivalent of food ingested and of urine and feces was determined daily for 80 days The animals, this time, were made to live at 30° C, 18° C, and 0° C, shaved and put to live at 18° C. and 8° C It is readily seen that there is a direct and proportional relationship between intake and

regulation is not sufficient to insure constancy of body weight and of body re-

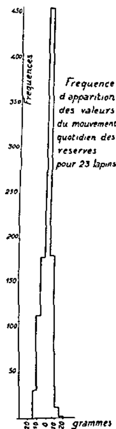


FIGURE 1 Illustrating the constancy of the dry weight (reserves) of animals maintained under uniform conditions (after Gasnier and A Mayer[4])

serves, as described in FIGURE 1. If there is oscillation of weight and reserves around a constant value (or, in other cases, around a steadily increasing curve) the "errors" of the day-to-day regulation must be compensated for through the action of a supervening regulation. In FIGURE 3, the daily values of "reserves" (body constituents other than water calculated around the privileged—most frequently encountered—value arbitrarily taken as zero) have been plotted in abscissae for the 23 rabbits for 80 days.[4] The ordinates are the variations of these reserves during the 24 hours immediately following their determination. All the points thus obtained are contained in the area defined by two hyperbolas (which are, in turn, characteristic of the limits of "homeometric variation" defined above). It is readily seen from the distribution of the experimental points within this area that, on a given day, the farther away from the "privileged" level the amount of reserves, the greater the chances that, during the next 24 hours, (a) if the variation is in the same direction, it will be small, or (b) if the variation is the opposite direction, it will be large enough to come close to, and even to overtake, the privileged value. Again, this variation is conclusive proof that, in the long run, as in the short run, variations of food intake are not haphazard but obey a stern underlying regulating mechanism.

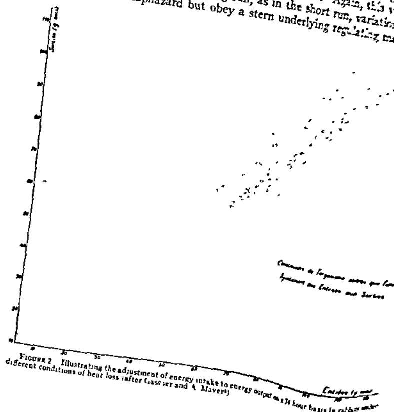


FIGURE 2. Illustrating the adjustment of energy intake to energy output on a 24 hour basis in rabbits under different conditions of heat loss (after Gasnier and A. Mayer).

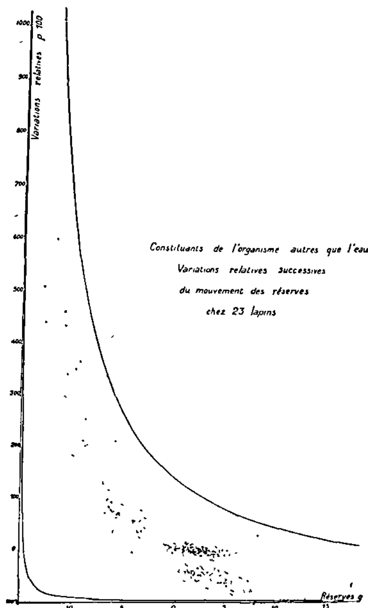


FIGURE 3 Abscissae values of reserves (nonwater body weight determined around the privileged value arbitrarily taken as zero) Ordinates variations of reserves during the 24 hour period following the determination of the abscissa Illustrates the long term regulation the more the value of reserves differs from the privileged value, the greater the chances that, in the next 24 hours, a large variation of opposite direction will occur, bringing body reserves back to the privileged value (after Gasnier and A Mayer[1])

III *Parameters of the Regulations*

Gasnier and A Mayer have defined the parameters of the two regulations, the regulation that, on a day-to-day basis, adjusts energy intake to energy output, and the regulation that corrects by "successive compensations" the short term mechanism[4] Such parameters, which in a given set of circumstances describe how well the regulations are performing their tasks, are (1) precision, (2) sensitivity, (3) rapidity, and (4) reliability

For the short term (day-to-day or energy regulation), the functional definitions of these characteristics are easily understood from the following statements:

(1) Precision—inversely proportional to the difference between energy intake and energy output

(2) Reliability—whatever the precision, if day-by-day the ratio were the same, the mechanism would be reliable

(3) Sensitivity—if the precision is dependent on the size of energy intake and output, then the sensitivity is variable

(4) Rapidity—the data presented in the various figures were established for a 24-hour period If adjustment of energy intake to energy output were better for shorter periods, rapidity would be greater

Similarly, for the long-term (long-range regulation of body reserves), the functional definitions of these characteristics would be as follows

(1) Precision—the precision is inversely proportional to the amplitude of the variation in dry weight which follows any observed value of body reserves More precisely, it is inversely proportional to the size of the area limited by the two hyperbolas and previously defined (FIGURE 3)

(2) Sensitivity is defined through the distribution of values around the "privileged" dry weight for which inversions have been observed

(3) Rapidity is inversely proportional to the time it takes, on the average, for inversions to take place

(4) Reliability is inversely proportional to the variation of body reserves during an arbitrary period The reliability implies the regularity of compensations in time, *i e*, their periodicity

These definitions make it possible to qualify numerically the two regulatory mechanisms For example, for the rabbits at 18 to 20° C, the short term (adjustment of energy intake to energy output) regulation is characterized by an average precision of 92 9 per cent; a reliability showing a maximum range of 64 per cent and an average variation of 18 5 per cent, and a sensitivity which seems constant within the range of intakes or outputs observed Incidentally, the characteristics of this short-term regulation of energy intake compare favorably with those of the day-to-day regulation of water balance

The long-term regulation by successive compensations has far less favorable characteristics: average precision, 27 5 per cent, average sensitivity, 27 4 per cent, average rapidity, 48 6 per cent It can be shown that, within this group of animals of the same weight and living in standardized conditions, there are marked individual differences (as well as marked strain differences if different strains are used) as regards the precision, reliability, *etc* of these two regula-

tions Some individuals consistently regulate their daily adjustment of en
intake to energy output, and their regulation of body reserves ("dry b
weight") better than others. The irregular animals are also the "big eat

IV *Factors Affecting the Regulations*

tion, it is indispensable to define the lapse of time considered All of us kı
and have known for a long time, that a large number of stimuli will transie
modify hunger and appetite and change momentarily the pattern of food
take: sudden exposure to heat or to extreme cold, necessity of violent exer
fear, rage, intestinal obstruction, gastric distension, appetite, depressant dr
toxic materials, *etc* A more pertinent question from the point of view no
events, but of regulations, is the effect of long-duration stimuli on the cl

studies of A Mayer[20] on changes in salinity and hydration, the studies
Adolph[19] and Kennedy[10] on changes in caloric dilution of the diet strikin
illustrate how these regulations, once temporarily disturbed, will settle afte

greatly from unity, this fact by no means signifies that they are not regulat
and parameters describing the two regulations can again be calculated.
shall come back to this important point later.

Two stimuli, temperature and exercise, have been examined with particu

as will be seen, is a transient effect with regard to heat (unless physiological
unendurable) Conversely, exposure to acute cold, after a short period
inhibition, will increase food intake as long as the animal is within the ran
to which it can become adapted Gasnier and A Mayer[8] have studied th
characteristics of both regulations, short-term and long-term, at various exper

TABLE 1

				(shaved)	(shaved)
Number of animals	4	4	8	4	3
Intake (cal /kg /day)	110 0	193 5	205 1	270 1	280 3
Variations of reserves (g /day)	−0 8	+1 0	+1.2	+1 7	+4 8

A similar picture is obtained when variations of exercise, rather tha environmental temperature, are used to obtain a range of metabolic in sities [20] FIGURE 8 gives the intakes and body weight obtained when va durations of daily exercise are forced on trained animals. While the pra of the exercise itself has an effect of immediately stopping the feeding pat

equilibrium has been reached, around a different body weight. Similar stu have been conducted in various forms of obesity[20, 14, 17] as well as on gr of human subjects [25]

It appears that it can be legitimately concluded from previous data and c ments that:

(1) There is a "biometric margin of variation" of energy intake and en output;

(2) There is a day-to-day adjustment of energy intake to energy outpu

(3) There is a long-term regulation of body reserves (or body weight);

(4) In both these regulations, one can define and calculate certain par eters, namely, precision, reliability, sensitivity, and rapidity. The long-t regulation is less precise, sensitive, or rapid than the short-term regulation.

(5) A number of factors that affect energy output also affect the equilibr position and the characteristic parameters of the regulation For exam

Ingestions par Kg.
et par jour.
Mouvement moyen des
réserves en fonction
de la déperdition

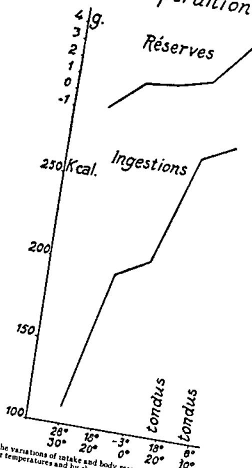


FIGURE 4 Illustrating the variations of intake and body reserves respectively as metabolic intensity is increased by exposure to colder temperatures and by shaving the animals (after Gasnier and A. Mayer[4])

cold (if not unendurable) will increase energy intake and output, and increase the size of body reserves It will increase the reliability of the day-to-day regulation of energy balance, increase the precision and reliability of the long-term regulation of body reserves, decrease its sensitivity and rapidity

(6) As mentioned before, the acute effect of many factors on hunger and

Précision des compensations successives du mouvement des réserves en fonction de la déperdition.

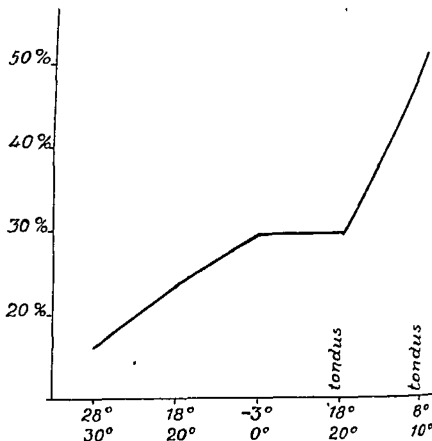


FIGURE 5 Variation of the precision of the short-term mechanism (daily adjustment of intake to output) as a function of metabolic intensity (after Gasnier and A Mayer[8])

appetite may be in a different direction from the long-term effect. Generally, such acute effects are inhibitory, while long-term effects may cause increase or decrease; for instance, bulk causes a decrease in intake which is temporary. Changes from high carbohydrates to high-fat diets cause a lag in response of adjustment of intake to output Both sudden exposure to cold and to heat inhibit food intake If these changes are outside the limits of adaptation, the eventual long-term effect is again deficit intake If the changes are within the limit of adaptation, the temporary drastic inhibition is followed by an increase up to lower than normal levels in heat, above normal levels in cold

(7) Obese animals, although their short-term regulation is adjusted (at least

V. *Mechanisms of the Regulations of Day-to-day Energy Balance and Body Weight*

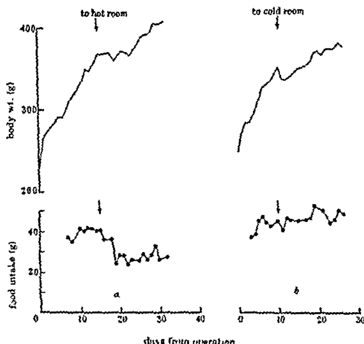


FIGURE 6 Effect of heat and cold exposure on weight and intake of hypothalamic hyperphagic rats (after Kennedy [10]) The animals were transferred from 75° F to 95° F and from 75° F to 34° F for a and b respectively

As regards the first mechanism, short-term regulation of energy balance, it should fulfill the following criteria:

(1) It must be integrated with the metabolic processes which mediate the relationship between energy intake and energy output. This means, in effect, that the mechanism has to be integrated with the regulation of carbohydrate, protein, and fat metabolism.

(2) It must have both anatomic and physiologic support. It must rest on known structures in the nervous system. It must be compatible with the known metabolic characteristics of the central nervous system and of these particular structures. It must be based on practicable and reversible cellular changes.

(3) It must be able to account for the effects of variations in environmental conditions associated with increased output (*e.g.*, cold, exercise) on energy intake, and must give an understandable metabolic interpretation of its adjustment to these conditions. Besides, it must be able to account not only for the changes in intake, but also for the changes in the parameters of the short-term regulation as well.

(4) It must account for the well-known effects on food intake of "metabolic" hormones, *e.g.*, insulin, growth hormone, thyroxine, *etc.*, and of disorders of

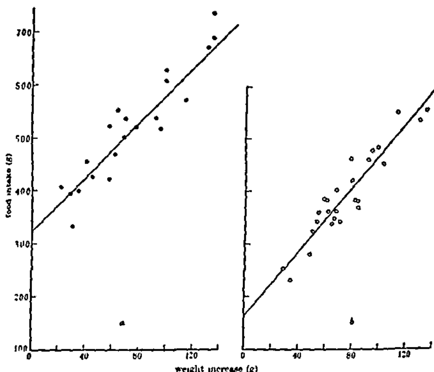


FIGURE 7. Linear regression of food intake on weight gain of hyperphagic rats during 14-day periods of maximal weight gain, *a* at 75° F., *b* at 94° F. (after Kennedy[19])

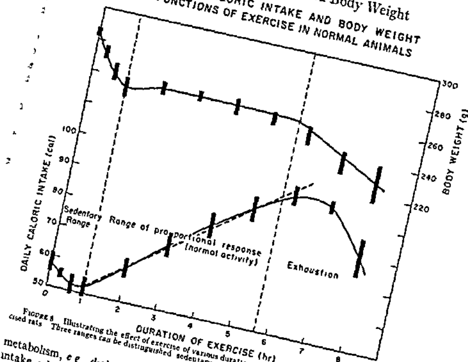


FIGURE 8 Illustrating the effect of exercise of various durations in caloric intake and body weight of exercised rats Three ranges can be distinguished sedentary, normal activity exhaustion (Mayer et al 30)

metabolism, *e g*, diabetes Also it has to account for those disorders of food intake which are clearly related to metabolic disorders, *e g*, "metabolic" obesity (like the endocrine-mediated hereditary obese-hyperglycemic syndrome of mice) It does *not* have to account for agents acting on the higher nervous centers, such as drugs, certain hormones—particularly those acting on electrolytes, nervous stimuli, psychic stimuli, or for purely nervous disorders of regulation (*e g*, "regulatory" obesity, probably exemplified by goldthioglucose obesity) Presumably, in all these cases, the agents are acting on the nervous regulatory system itself rather than on what it is that the centers regulate These factors will be reviewed by Doctor Brobeck

(5) Finally, it is well understood that any theory of short-term regulation which does not account for the existence of the hunger state and its opposite is doomed at the outset While the mechanism has to account for the existence of the hunger state (including gastric pangs) and give a physiologic framework for the hunger behavior, it does not have to account for either consciousness of hunger or for feeding behavior at a given time Both of these can be influenced by a multiplicity of other factors and are, again, central phenomena On the other hand, the mechanism must account for the frequent (at least daily) occurrence of meals

We believe that only a mechanism based upon variations of available carbohydrates fulfills these five criteria, and we shall give experimental evidence which supports the existence of such a mechanism

As regards the second mechanism, that of regulations of body reserves (weight), such a mechanism would have to fulfill the following criteria:

(1) It must account for the constancy of body weight of normal individuals under a given set of circumstances over a long period of time, as well as for the fact that weight loss due to fasting or underfeeding is followed by the recovery of the "privileged" body weight

mal" weight *and to be regulated for that weight.* In particular, it must account for the fact that obese animals submitted to weight loss through fasting or underfeeding regain the "privileged" obese weight as soon as limitations to intake are removed.

(4) It must account for the transition in several types of obesity, in particular of the "regulatory" type, from the "active" phase of obesity characterized by

amount of fat mobilized daily to size of depot fat, the coefficient of proportionality being characteristic of each type of animals and of environmental circumstances, could fulfill all five criteria. We shall mention experimental data which make the existence of such a mechanism not unlikely.

VI. *Glucostatic Mechanism of Regulation of Energy Intake*

According to the glucostatic theory, the mechanism postulated for the short-term regulation of energy intake rests on the concept that somewhere, pos-

concept fulfills the five criteria set up for the short-term regulation.

(1) *Integration with over-all metabolism, with carbohydrate, fat, and protein metabolisms.* It is well known that carbohydrate metabolism plays a central role in the regulation of energy metabolism. The stores of carbohydrates are small (75 g in the liver, only a little more in the muscles). Blood glucose is utilized preferentially by all tissues and exclusively by the central nervous system. There is a formidable system of nervous, hormonal, and humoral mechanisms all designed to maintain the homeostasis of blood sugar. Prevention of low values is of vital necessity for the organism, as it causes death through incapacitation of the central nervous system. Emergency mechanisms, such as the action of epinephrine, or of longer lasting palliatives such as

gluconeogenesis, will prevent hypoglycemia but, in the last resort, only the partaking of food will restore full homeostasis It is all the more necessary that, whenever the environment forces a greater expenditure of energy, the first substrate which tends to become depleted is carbohydrates. Protection against excessive values of blood glucose, though less urgent as regards function of the central nervous system and life, is necessary to avoid damage to certain structures, such as the pancreatic islets and the kidneys, and is essentially effected by the conversion of carbohydrates to fat and the increased combustion of carbohydrates. Carbohydrate metabolism, besides being regulated by an architecture of endocrine organs is itself the regulator of fat and protein metabolism Geyer[26] has shown that availability of carbohydrates decreases fat utilization and that lack of carbohydrates causes an automatic and quantitatively determined increase in fat oxidation Engel[27] has shown that the availability of carbohydrates similarly conditions gluconeogenesis The crucial role of carbohydrates in the economy of the central nervous system, the lack of its storage, its preferential utilization, the thoroughness of its regulation, and its role, in turn, as the central regulator of over-all metabolism are telling arguments for claiming that a regulation based on carbohydrate, and only such a regulation, can successfully be integrated with energy metabolism and its components

(2) Material support of the regulation Possible anatomophysiologic support for the regulation is provided by a number of facts Allusion has already been made to the special importance of carbohydrates in the economy of the central nervous system More specific facts are as follows

First of all, the existence of glucoreceptors in the central nervous system has been indirectly demonstrated in connection with other physiologic phenomena Thus, the test for effectiveness of vagotomy has long been the examination of the response to insulin, vagotomy abolishing the normal gastric response to hyperglycemia[2] The work of Zunz and La Barre[28] showed, as early as 1927, that, when the circulation of a dog's head was isolated from the rest of the body, with the nerve supply from head to body intact, hyperglycemia of the head resulted in hypoglycemia of the body, a finding recently confirmed and interpreted by Duner.[29]

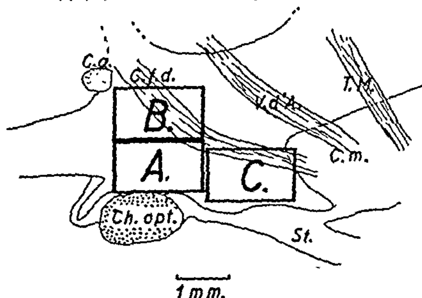
It would be tempting to interpret the demonstration of special receptivity to glucose and phosphorus of the hypothalamic feeding area as support for the glucostatic concept This investigator is both gratified and honored that, in the introduction to their excellent work on "isotope distribution and chemical composition in the hypothalamic region of hungry and fed rats," Forssberg and Larsson[30] were kind enough to write (p 41) · "the finding that in the hypothalamic region a structure is present which in some way regulates the sense of hunger and which, according to Mayer *et al* (1952) is the site of so called receptors ('glucoreceptors') encouraged us to the following biochemical approach to the problem " The fact that this approach met with a measure of success suggests that the glucostatic concept, whatever its eventual fate, will have been of some use Larsson and Forssberg reasoned that the hunger state must be accompanied by changes in the concentration of those compounds through which brain tissue, which cannot burn or store fat, can achieve, nevertheless,

some energy storage, *i e*, phosphagens: creatine phosphate and adenosine triphosphate. Rates of incorporation of glucose and phosphorus would be expected to be particularly affected in the feeding center area if these centers

jected that behavior of appetite under such conditions as diabetes mellitus made it probable, in the light of a glucostatic concept, that the metabolism of that particular area would be found to participate to some of the characteristics of nonneural tissues, in particular, liver; a concept supported by the findings of Larsson) To account for this specificity, Forssberg and Larsson studied isotope incorporation, not only in the feeding center area, but also in other hypothalamic areas (*A* and *B* in FIGURE 9). Blood, liver, muscle, and cerebrum were also studied

The results showed that, in hungry rats, the sample *C*, which includes the feeding centers, shows a preferential uptake of ^{32}P, indicating an increased physiological activity over that in the fed state. By contrast, in the fed state, activity of regions *B* and *A* is enhanced, while that of *C* is proportionately decreased. Total activity in the hypothalamus stays the same, activity in the blood and cerebrum is also unchanged, indicating the specificity of the behavior

relationship playing the central role Pilot experiments with ^{14}C-Glucose show



the same type of response. In hungry rats, the feed- … more
receptive to glucose, as compa… The
liver, incidentally, show… C-Glucose
in the hunger state than … these facts could be taken to support
the contention that there is anatomic and physiologic support for the glucostatic concept. It is not claimed by this investigator, however, that the receptors are exclusively or even necessarily in that particular area. It may well be that there are peripheral as well as central glucoreceptors, and even that the hypothalamic feeding area is only a relay. It may be recalled, in this connection, that there is still some doubt as to the precise localization and cellular structure of osmoreceptors and central thermoreceptors.

(3) *Effects of increased energy out…*
both in the cold…
of carboh… to increase
intake by … reserves at all times (unless fre-
quently ar… ly replaced), but also, as a result of the more rapid turnover and tendency to depletion of the stores, to decrease the margin of variability and thus increase the reliability of the regulation. A similar situation may prevail in growth.

The temporary decrease in food intake which follows shift from a high fat to a high carbohydrate diet may represent a lag in enzymatic or hormonal readjustment to the burning of a different metabolic mixture. The same explanation would explain the increase in food intake when the animals are switched from a high carbohydrate to a high fat diet. "Sparing" the carbohydrates would necessitate tissue, hormonal, *etc.*, readjustments which would take time. Until these results are achieved, excessive carbohydrate utilization would cause excessive eating.

(4) *Effects of metabolic hormones and disorders of metabolism.* Insulin treatment first causes a fall in blood sugar due to increased peripheral utilization of glucose. In a second phase, a compensatory rise takes place which is secondary to decreased utilization in the periphery.[33, 34] The increase in food intake following insulin administration is thus readily interpreted (incidentally, amphetamine curbs the increase in appetite induced by insulin, illustrating the difference between "metabolic" and "regulatory" agents).

The apparent paradoxes afforded by the hyperphagia of diabetes mellitus, by the phenomenon of hunger diabetes, by the hyperphagia accompanying the high blood sugar in certain types of obesity can likewise be interpreted in the light of decreased utilization, readily demonstrable by consideration of arteriovenous glucose differences or uptake of inorganic phosphate. In hyperthyroidism, alimentary hyperglycemia typically occurs and is followed regularly by a postalimentary hyperglycemia. It has been suggested[34] that accelerated metabolism of glucose takes place in the hyperthyroid patient, and that the alimentary hyperglycemia may be only a manifestation of starvation diabetes following rapid depletion of carbohydrate stores. It appears that the increased food intake characteristic of hyperthyroidism may thus again be related to metabolic hyperglycemia. A possible interpretation of the effect of growth hormone on appetite can also be derived from its known physiology.

The effect of epinephrine deserves special mention, as it represents an apparent exception to the general rule Epinephrine administration causes an immediate increase in blood glucose, and it drastically reduces or eliminates any effect of hunger At the same time, however, it decreases peripheral

animals demonstrate that, while it decreases peripheral Δ-glucose values, it increases carotid-jugular glucose differences, thus not only does it produce hyperglycemia, but it increases the proportion of glucose made available by the nervous centers. It has recently been indicated[35] that *in vitro* glucose consumption of hypothalamic tissue is increased within a few minutes after the administration of epinephrine

Furthermore this hormone has a number of other effects which may intervene at higher (central nervous) levels and not be related to the metabolic substrate

pituitary tumors should provide some data toward the solution of this important question.

(5) *The hunger state and hunger behavior.* Finally, there is still a need for

deficiency The often demonstrated similarities between caloric deprivation and diabetes emphasize the dominant role of reduced availability of carbohydrates in the fasting state Because of the limited supplies of carbohydrates in the body, it is to be expected that frequent meals will be necessary to replenish the reserves, particularly in herbivorous animals In carnivorous animals, the high protein intake may lead to a decreased frequency of meals for a variety of reasons (slower absorption, steadier utilization, satiety effect of amino acids, possibly, in part, pharmacological effects of decarboxylated products) Because lack of available carbohydrates itself initiates gluconeo-

was found that the arteriovenous glucose differences, if determined with prope
analytical care, gave an easily obtainable and generally reliable representatio
of glucose utilization More detailed data on the limitations of the use o
Δ-glucose as a measure of utilization of carbohydrates have since been experimentally obtained and the conclusions discussed by Doctor T. B. Van Itallie [37] These studies further demonstrated that the "hunger state" as defined previously[4] is, physiologically speaking, the state in which peripheral arteriovenous glucose differences tend toward zero It may be added that the definition is equivalent to one which would define the hunger state as the state in which the respiratory quotient tends toward the values corresponding to the burning of fat Diabetes mellitus, hunger diabetes, are, then, characterized as conditions in which the "Δ-glucose" are small unless the absolute level of blood glucose is pushed to a very high level by additional ingestion of food *In effect, any state for which there is an appreciable Δ-glucose is a state where glucose is utilized or stored into fat and cannot therefore be a hunger state. To claim the contrary would be to end up with a definition of the hunger state compatible with a high R Q*

It is my hope that it is unnecessary to reiterate that the presence of the hunger state is not a necessary guarantee of feeding behavior We have mentioned often enough the factors which, at a given time, will lead to those states which Janowitz and Grossman[3] have called hunger state without the desire to eat or without the intake of food (anorexia or hyporexia) Similarly, hyperorexia can occur To be convincing, however, the glucostatic definition of the hunger state must be generally accompanied by the desire to eat, that of the satiety state, by the absence of this desire Experiments illustrated in FIGURE 10 and reported in detail elsewhere[38] have shown that this was generally the case in man FIGURE 11 is an illustration of the fact that the evolution of inorganic phosphate is an equivalent method of study,[33] a finding which is of interest in the light of the subsequent data of Forssberg and Larsson [39]

Doctor Stunkard has since had occasion to show that there was a good degree of correlation in man between small Δ-glucose and the appearance of subjective hunger in man, between large Δ-glucose and the absence of these feelings He has further shown, using the intragastric balloon technic, that the appearance of hunger contractions was well correlated with vanishing Δ-glucose, an observation that fulfills one of the important subcriteria that we have set up [42] He has demonstrated that slow intravenous glucose infusion in hungry individuals eliminated both the feeling of hunger and stomach contraction except in diabetic subjects where the impairment in glucose utilization was demonstrated by a rise in blood-glucose level without a coexistent increase in Δ-glucose values FIGURES 12 and 13 will serve to illustrate these points * Finally, in a neat demonstration of the fact that psychologic factors operate within a physiologic

* Inhibition or increase of food intake of animals submitted to various conditions of modifications of carbohydrate metabolism also illustrate the point though it must be pointed out that in our experiments,[40] intakes were never determined on less than a 24 hour basis, and therefore do not actually constitute a study of the relation of the state of carbohydrate metabolism at a given time with the feeding pattern at that time Learning processes then would play an important role particularly in animals such as dogs, which exhibit strongly "learning" or "conditioned" behavior This fact may explain some apparent contradictions in published experimental results [41] It may be remarked, in passing, that studies on the effect of glucose infusions on appetite in man or dogs run into the conditioning problems which have already been mentioned As the findings may seem contradictory to results reported in the literature, it may be useful to remind the audience of the long-term observations of Albright.[44]

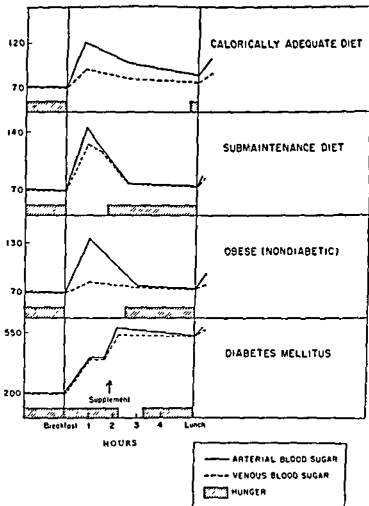


FIGURE 10 Correlation of Δ glucose and hunger feelings Composite scheme illustrating the statistical correlation of morning Δ glucose and feelings of hunger (Mayer[38])

framework, Doctor Stunkard has shown that hunger feelings and hunger gastric contractions could be induced by psychologic stimuli (*i e.*, talk, sight, or smell of food) provided a small Δ-glucose testified to the existence of a hunger state as defined in the glucostatic sense.

It may be remarked that the restlessness and increased activity characteristic of "hunger behavior" is a universally observed consequence of metabolic hyperglycemia. Even unicellular organisms such as *Stentor* have been shown to stop the quiescent state as reserve granules disappear.[43] It appears there-

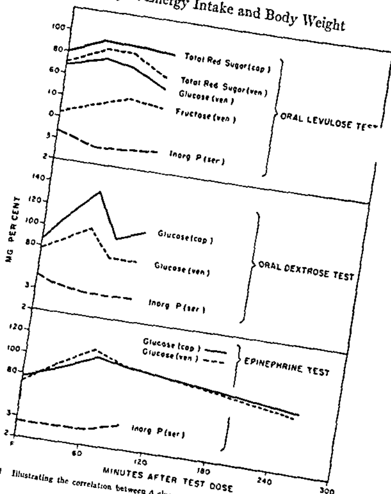


FIGURE 11 Illustrating the correlation between Δ glucose and serum inorganic phosphorus variations (Beaudoin[?])

fore that the glucostatic mechanism fulfills the criteria set up for acceptability as the mechanism of the short-term adjustment of energy intake to energy output It is hardly necessary to labor the fact that previously proposed alternative theories failed to fulfill most of the criteria Basing the regulation on epigastric pangs was *ipso facto* invalidated when it was shown that vagotomy, which abolished the contractions, splanchnectomy, which abolishes their sensation, or even gastrectomy did not significantly alter the characteristics of the regulation[8] As the possible role of hypoglycemia had been raised al... exclusively as a factor working through gastric phenomena, its st... pursued no further, especially in view of the lack of correlation en...

GLUCOSE MG %
210
180
150
120
90
60

IL 27 ♂
3-29-54

ART
VEN

GASTRIC CONTRACTIONS
HUNGER
GLUCOSE
TIME IN MINUTES 25G IV 10 20 30 40 50 60

FIGURE 12 Hunger feelings and hunger gastric contractions as affected by intravenous glucose infusions in a normal man (Stunkard, personal communication and in press)

GLUCOSE MG %
270
240
210
180
150

MB 26 ♂
3-11-54
DIABETIC

ART
VEN

GASTRIC CONTRACTIONS
HUNGER
GLUCOSE
TIME IN MINUTES 25G IV 10 20 30 40 50 60

FIGURE 13 Hunger feelings and hunger gastric contractions are not abolished by intravenous glucose infusions in a diabetic subject (Stunkard, personal communication and in press)

between hunger and absolute levels of blood glucose[45] and the then apparently unsurmountable difficulty of diabetic hyperphagia

A "thermostatic explanation" such as that suggested by Brobeck and [illegible]

species (e g , rats[48]) become warmer when fasted.

VII *Regulation of Body Weight a "Lipostatic" Hypothesis*

It has been shown, in a previous section, that there is a regulation of body [illegible]

mals there is a "privileged" body weight depending on the type of animals, individual physiologic characteristics, diet, exercise regime, and even individual taste preferences The parameters of this regulation have been defined previously, the effect of at least two factors mentioned Criteria that any proposed mechanism would have to fulfill have been set While the glucostatic mechanism is an attempt to give a coherent interpretation for the short term regulation, and is supported by some experimental data, no such theory has been formulated for the long-term regulation In the absence of sufficient evidence, it would appear unwise to elaborate at length on what, at the present time, is no more than a working hypothesis The problem, however, is of such importance, and has gone so largely unrecognized that formulating the hypothesis would at least help to define the problem Because the size of the fat depots of normal and obese animals seems to determine the return to the priv- [illegible]

any increase in fat content being followed by increased availability of readily utilizable fat, with consequent sparing effect on carbohydrates;

(2) Account for the effect of various long-lasting stimuli on body weight because of their demonstrated effects on fat mobilization and turnover;

(3) Account for similar phenomena in obesity. Our studies of fat synthesis and fat mobilization in various types of obesity show that, while each type is characterized by different idiosyncrasies, these types are well defined and regulated For example, in the hereditary obese-hyperglycemic syndrome there is drastically increased synthesis independently of increased caloric intake.[50, 51, 52] This increase is not found in goldthioglucose or hypothalamic obesity The latter, in the dynamic phase, shows extremely reduced fat mobilization under *conditions of ad libitum feeding*[49]

(4) This mechanism could account for the fact that "static obesity" is accompanied by a decrease in food intake from the high values in "dynamic obesity," and that these values are restored by fasting Considerations of energy expended in activity do not permit interpretation of this striking observation, because the activity in many types of obesity is so small, in the first place, that increase in cost of work with weight is negligible because of lack of movement.

(5) Because of the interrelationship of carbohydrate and fat metabolism, the lipostatic hypothesis could be integrated with the glucostatic mechanism. The long-term regulation would function (as in fact it does), by correcting the short-term mechanism

The glucostatic theory has been attacked, not infrequently, by attributing to it claims it had never made and then disproving these claims. The theory never claimed to be able to interpret the initiation of eating at a given time because habits, learned behavior, taste, extraneous factors such as sudden exposure to

vene, but sir

after these ef

of the temeri

hypothesis,

permissible to end this discussion on a slightly rueful note, its reception has illustrated to a certain extent the fate which, William James warned, awaited all new concepts "First people say it is not true; then they say it is of no general significance, and finally, they say that anyway it had been known for a long time" It may well be, as a matter of fact, that all these criticisms are well founded. At any rate, what the eventual fate of the theory is going to be and what lasting value, if any, it will achieve will be inexorably decided by the test of time.

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NEURAL REGULATION OF FOOD INTAKE*

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Nearly all of the published studies of the regulation of food intake neglect the fact that the total amount of food eaten is always the product of two factors, the number of meals multiplied by the intake of the average meal. This is true for any animal which eats periodically, as most of the higher animals do, and it applies equally to short-term experiments of a day or two, or to long-term studies lasting many months Any procedure altering food intake does so through some change in one or both of these, while any constancy observed in intake from time to time is a result either of a uniformity of frequency and

ince all behavior in higher animals issues from the central nervous system, it eems appropriate to attempt to review what is known of the central mechaisms taking part in this regulation.

For a time, the central components of hunger, appetite, and satiety were eglected because of emphasis upon the gastric origin of hunger, although this

Carlson (1916, p 215) to have discovered that the hunger behavior of decortiated pigeons is abolished by removal of the optic thalamus, *i e*, the hypoalamus It now seems probable that the gastric mechanism was overemhasized because it could be studied rather easily, and much was learned about

Moreover, observations upon vagotomized subjects and animals with enervated gastric pouches implied that the origin of the contractions was dependent of central nervous control For many years, the central nervous

at appropriate injury to the hypothalamus causes aphagia as well as hyperhagia, it was clear that the brain possesses mechanisms for both starting and opping eating behavior

These discoveries that the hypothalamic mechanism is a dual one suggest at "appetite" and "satiety" may be two separable and distinct phenomena ppetite and satiety are used here in a purely behavioral sense, without prejdice as to their subjective or psychological nature) If the region where

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injury causes aphagia is an appetite mechanism, then its overactivity will increase food intake, while its underactivity will reduce it. Similarly, if the region where lesions cause hyperphagia is a satiety mechanism, then its underactivity will lead to overeating, while its overactivity will decrease food intake. These predictions are in agreement with the results of Miller, Bailey, and Stevenson (1950), who found that rats with hypothalamic hyperphagia show a decreased satiety, but no increase in appetite as measured by their willingness to work for their food or to eat food of unpleasant taste. There may be, therefore, four possible states of the animal with reference to feeding behavior, namely, (1) a state of increased appetite and (2) one of diminished satiety, both of them leading to overeating, (3) a state of reduced appetite, and (4) one of enhanced satiety, both tending to limit the amount of food taken. The first two of these states will be reflected in a larger intake per meal and/or a shortened interval between meals, while the second two will cause a reduced intake per meal and/or a lengthened interfeeding interval. Other characteristics of the four states and their interactions may be discovered when they have been studied more adequately.

Now that the importance of the central nervous system is agreed upon, one may attempt to make use of what is known about the nature of central nervous mechanisms in an attempt to understand better the basis of feeding behavior. Every one of the functions of the brain and spinal cord that has been studied successfully has proved to have an important substructure of reflex actions, completed through connections in spinal cord, brainstem, or even via the cerebral cortex. This statement applies to the maintenance of tone in skeletal muscle, to posture, to locomotion in laboratory animals, to control of respiration and circulation, and to other forms of activity in autonomic and visceral portions of the nervous system. Superimposed upon these reflexes, the tegmentum of the brainstem, the diencephalon, and the telencephalon express their own potentialities by either facilitating or inhibiting the lower motor neurons (or the interneurons) belonging to the reflex arcs. Certain of the higher centers are believed to possess activity of intrinsic origin, analogous to the intrinsic activity in cardiac or smooth muscle. In the case of the brain, however, this point is not settled, and it may turn out that what appears to be intrinsic is merely prolonged or delayed reflex activity. Whatever its origin, the effect of the higher upon the lower mechanisms is obvious in many cases, central facilitation and inhibition are real phenomena, and the importance of the final common pathway and of reflex arc is beyond dispute.

It has often happened in neurophysiology that a study of behavior is made easier if the reflexes upon which it is based can be identified and classified. Thus, the spinal reflexes described by Sherrington, the postural reflexes of Magnus, the righting reflexes classified by Magnus and Rademaker together with the placing and hopping reactions studied by Bard—all of these have contributed to our understanding of the mechanisms of posture and locomotion. One could make a similar statement about the reflexes concerned with movements of the eyes and control of the intrinsic muscles of the eye, or with reference to pulmonary ventilation, vasomotion, and the rate of the heart. I

appears that feeding reflexes have not been presented in this manner, and no catalogue of these reactions is available. Two different patterns of classification suggest themselves One is based upon the nature of the stimulus inducing the reflex, as in the righting reflexes; the other considers mainly the motor act resulting from the reflex, as in Sherrington's description of flexor and crossed extensor reflexes.

In terms of the stimulus causing the response, feeding reflexes belong in the following categories:

(1) Visual feeding reflexes are initiated by appearance of an object in the animal's field of vision. These reflexes probably require connections through the cerebral cortex, resembling, in this respect, the more familiar accommodation reflex of the pupil of the eye.

(2) Olfactory feeding reflexes likewise possibly involve cortical mechanisms.

(3) Auditory feeding reflexes may have also a cortical component.

(4) Tactile feeding reflexes are typified by the reflex noted in human infants, where a baby turns its head when a hand or flat surface is placed against the cheek (Aldrich, 1942) Tactile reflexes also include grasping, sucking, and swallowing reflexes seen in babies, and the chewing and swallowing reflexes observed in decerebrated animals (Miller and Sherrington, 1916). Some of the rejection reflexes mentioned below are no doubt stimulated by objects of undue hardness or sharpness, or by objects having some other quality perceived by the sense of touch.

(5) Gustatory reflexes are also concerned with sucking, chewing, and swallowing, as well as with secretion of digestive glands and motility of smooth muscle in viscera They, too, include rejection reflexes

(6) Enteroceptive reflexes are more difficult to list. Distension of the stomach or duodenum is known to induce reflex actions, as does the cramplike contraction of a gastric hunger pang

This listing is not complete, since it does not attempt to include other reflexes not restricted to feeding mechanisms, and yet capable of affecting them.

A second classification of the same reflexes, but based upon the nature of the response, is more difficult to prepare. The following is only a tentative outline:

(1) Reflexes of attention serve to focus a sensory system upon the source of the stimulus

(2) Reflexes of approach include those producing locomotion, or even the turning of the head or the mouth toward the source of food.

(3) Reflexes of examination allow the animal to investigate the edibility of an object

(4) Reflexes of incorporation include those which evoke chewing and swallowing

(5) Reflexes of rejection prevent eating of inedible or otherwise unacceptable objects.

Some of these reflexes—for example, chewing and swallowing—occur in decerebrate preparations Others must require the participation of at least the primary sensory cortex, while the first three and the last categories include

behavior often considered to be "voluntary" Further study may enable us

inhibitory one for feeding reflexes Since Anand and Brobeck (1951) found that the destruction of both mechanisms always results in a failure of feeding, their observations offered the possibility that the medial mechanism acts to inhibit the lateral one This possibility, however, was not established by their experiments, and there is one other type of evidence which implies that both of the hypothalamic mechanisms exert their effect at levels lower in the brain-stem *Ruch, Patton, and Brobeck (1942) noted in monkeys that obesity* followed injury confined to the rostral part of the tegmentum of the mesencephalon, a region removed some distance from the location of the ventromedial nuclei of the hypothalamus If the medial mechanism (the "satiety center") in the region of the ventromedial nuclei directly inhibited the mechanism in the adjacent, lateral hypothalamus (the "appetite center"), it is difficult to understand how lesions in the mesencephalon could interrupt the fibers mediating the inhibition It seems more likely that the inhibitory fibers descend from the medial portion, while the facilitatory fibers descend from the lateral portion, and that both of them have their actions upon motor or internuncial neurons of the pons, medulla, and spinal cord

Another important characteristic of feeding behavior is the increase in locomotor activity which anticipates feeding (Rogers, 1916, Richter, 1922) or accompanies complete or partial starvation (Wald and Jackson, 1944) Hyperactivity has been observed, also, in animals with operations upon the central nervous system Richter and Hawkes (1939), and Ruch and Shenkin (1943)

that lesions in the tuberal portion of the hypothalamus lead to a reduced activity Some of the animals studied by Hetherington and Ranson ate at least a normal amount of food, while a few of those in the author's laboratory have exhibited hypophagia and hypothermia along with the hypoactivity Sometimes one obtains animals that have normal activity with hyperphagia, while Anand and his colleagues (1955) have described what appears to be normal activity with aphagia There seems to be no necessary correlation, then, *between deficits of regulation of activity and of food intake in animals with*

ventromedial nuclei (Hetherington and Ranson, 1942, Brobeck, Tepperman, and Long, 1943)

Since hyperactivity and the onset of feeding are related under natural conditions, it is a little surprising that there is not more regularity in the data just reviewed. In many of the experiments where activity was recorded, however, the food intake was not carefully measured, while most of the studies on feeding deficits have been done without objective measures of activity. A more thorough study may resolve some of the present inconsistencies. Nevertheless, there seems to be little question that the brain, probably within the hypothalamus, contains a mechanism which may impel the animal to move about from place to place. This mechanism is presumably released from inhibition by lesions in the frontal cortex, caudate nuclei, or rostral hypothalamus (Rogers, 1916), but it may be injured or destroyed by operations upon the tuberal hypothalamus. A similarity between the organization of this system and the mechanisms regulating feeding is apparent. It will become even more striking if confirmation is obtained for a recent report that, in normal animals, the hyperactivity of food deprivation is reflex in origin (Campbell and Sheffield, 1953).

A simplified explanation, though not proved to be correct, of the effect of hypothalamic injuries upon feeding behavior is that when food is eaten by a normal animal, there occur within the body certain changes which either directly or indirectly affect the hypothalamus. These changes serve as signals to the brain, tending to suppress the activity of the lateral hypothalamus and thus to decrease appetite, while they stimulate the medial or inhibitory portion of the mechanism and thus promote satiety. As the food is disposed of through conversion to heat, or work, or some form of stored energy, the changes produced by the feeding tend to disappear. Now the lateral hypothalamus becomes more active, while the medial hypothalamus is inhibited. At the same time, the animal's locomotor activity begins to increase. In this manner, the animal is brought into an environment where food may be found, where the facilitation of feeding reflexes and a removal of their inhibition will lead to the investigation and eating of the food. One may explain, in this way, the feeding behavior of animals living where good food is always available—an ideal situation, yet a basic one (and less complicated than any experiment where a "specific hunger" is involved). Under the conditions just stated, an animal, for much of the time, behaves as though unaware of the food; that is, the presence of the food, its odor, *etc*., stimulates no food-directed behavior. The animal may even resist attempts to feed it, or to induce it to eat by placing it near the food. Later, all of this changes, and the animal becomes active, investigative, and ready to eat. If food is withdrawn, the activity is still further increased, and other types of behavior become evident, including the investigation and chewing of inedible objects. It is this type of behavior that is so dramatic immediately after the operation that induces hypothalamic hyperphagia in rats. First, there appears to be a striking hyperactivity, well before the animal is able to right itself completely and walk normally. This develops into an abnormal tendency to investigate objects in the cage. At this stage, the animal

does not eat, but moves almost continually, using its nose to turn over and momentarily examine each piece of food Within a few minutes, the food begins to be accepted, and soon the animal eats ravenously, although not continuously If a soft diet of acceptable composition (Kennedy, 1950) is presented at this point, the animal may eat a tremendous amount For example, F. Brooks has recently observed overnight a weight gain of 49 gm in a rat originally weighing 249 gm (unpublished) If this same food is offered earlier, the animal first walks through it or over it without appearing to be aware of the food Later, it pauses to examine the food but does not eat Still later, but before the onset of definite hyperphagia, it eats small amounts each time the food is encountered, as the animal wanders around the cage [illegible]

is upset and over-facilitation occurs In later stages, after the animals have become obese, as Kennedy (1950) has emphasized, the hyperphagia becomes much less obvious, and the food intake may approach the normal level But if such an animal is starved, so that its body weight returns to that of a control rat, hyperphagia will reappear during refeeding (Brobeck, Tepperman, and Long, 1943) If the operation has abolished a satiety mechanism, as the work of Miller *et al* (1950) suggests, then, after the animal recovers from the acute stage, its regulation must take place solely through variations in appetite, much as one might control the speed of a motor car entirely with the accelerator after the brakes had failed

[illegible] awake and active, did not show any neurological deficits, and their rectal temperatures were normal They refused food not only when it was placed in contact with their lips and teeth, but even when it was placed inside their mouths" (p 144) Writing of their monkeys, they stated "In four monkeys the operations were followed by complete cessation of eating and they would not eat even when the food was put into their mouths Two other monkeys on the other hand, would not eat the food easily available to them in the cage, in spite of starvation, but when the food was put directly into their mouths they would bite on it and swallow it These two could be kept alive by putting the food into their mouths, while the other four had to be fed by stomach tube" (p 147) *From their observations, Anand and his*

[illegible]

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normal balance between facilitation and inhibition at the hypothalamic level In other words, the function of the hypothalamus as an integrating mechanism is upset and over-facilitation occurs In later stages, after the animals have become obese, as Kennedy (1950) has emphasized, the hyperphagia becomes

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Animals with hypothalamic aphagia are quite different, and show no interest in food Anand *et al* (1955) have described the behavior of their cats as follows " except for aphagia, they did not seem to be abnormal They were awake and active, did not show any neurological deficits, and their rectal temperatures were normal They refused food not only when it was placed in contact with their lips and teeth, but even when it was placed inside their mouths" (p 144) Writing of their monkeys, they stated "In four monkeys the operations were followed by complete cessation of eating and they would not eat even when the food was put into their mouths Two other monkeys .. on the other hand, would not eat the food easily available to them in the cage, in spite of starvation, but when the food was put directly into their mouths they would bite on it and swallow it These two could be

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of all such reflexes. This seems to confirm the concept stated above, that the hypothalamus is not a direct part of the reflex mechanisms, but that it acts to inhibit or to facilitate the reflexes. Animals suffering from aphagia show behavior typical of satiety in normal animals, and it is difficult to escape the conclusion that they are satiated through (1) the removal of the neural circuit responsible for appetite and (2) through the resulting, unopposed action of the mechanism causing satiety. In general, the concepts presented here follow the views of Strominger and Brobeck (1953) regarding feeding behavior, and the hypothesis presented by Stellar (1954) to account for motivations of all types.

Before closing my discussion, I wish to comment on three other features of the mechanisms regulating food intake. The first is the nature of the change which signals to the regulating system that feeding should be stopped after food has been taken within the body. Among the changes considered by various authors are the availability of glucose in body fluids (the glucostatic hypothesis of Mayer, 1953), the concentration of certain metabolites, as yet unspecified (the lipostatic hypothesis of Kennedy, 1950), the water concentration, or shifts of water among the compartments within the body and lumen of the digestive tract (suggested by experiments of Adolph, 1947; Strominger, 1947, Cort, unpublished, and others), and sensations from the upper digestive [illegible]

feeding. These authors also wrote, however, "Other factors undoubtedly exist, with the result [illegible]
the integration [illegible]
organism and [illegible]
should be emphasized, because there has been a temptation to fix upon some one change, and to try to explain everything with reference to one hypothesis. The ingestion of a single food brings about such a multitude of changes within [illegible]

of its digestion are amino acids and peptides, or monosaccharides, or fatty acids, glycerol, and neutral fats. Since there is this variety of changes brought about by feeding, it is not surprising that more than one of them can provide signals to the regulator, nor is it remarkable that no one hypothesis has proved to be entirely satisfactory. The idea presented by Janowitz and Grossman (1949), a multiple factor theory of regulation, appears to offer the only logical resolution of present controversies.

A second point of interest is the problem of whether the hypothalamus contains the cells which are sensitive to the signals that have just been considered. Many authors have assumed that it does, in the same way that the respiratory complex of the medulla oblongata is believed to be sensitive to changes in carbon dioxide tension and pH. In the case of the hypothalamus, there ap-

pears to be no direct evidence for such a specific sensitivity as a factor concerned with either appetite or satiety. In all probability, the neurons of this part of the brain share the properties of nervous tissue in general and are affected by hydrogen ion concentration, oxygen lack, carbon dioxide accumulation, hypoglycemia, *etc*, yet the only one of these disturbances to which a specific sensi- [illegible] specific sensitivity Since there is no conclusive evidence that the hypothalamic cells serve as sensory endings in regulating feeding, one may well recall that all that is definitely known about this regulation can be accounted for on the ground that the hypothalamus is an integrative center for impulses brought into the nervous system from sensory cells in other parts of the body, rather than a site of the primary receptors The notion that the hypothalamus is sensitive, however, is an attractive one, and is so well established that it may be difficult to dispel from our thinking Jolliffe (1952) has even given a name to this hypothetical mechanism, calling it the "appestat"—a name which has been widely used in both scientific and popular literature Whether the hypothalamus does, indeed, respond directly to some change, there is definite evidence that other sensitive cells do participate in the regulation Receptors in mouth, pharynx, esophagus, and stomach are stimulated while food is being eaten, and Janowitz and Grossman (1949) have shown that both the mechanics of feeding and the presence of food within the stomach are important factors in regulating food intake Unpublished experiments by Cort (FIGURE 1)

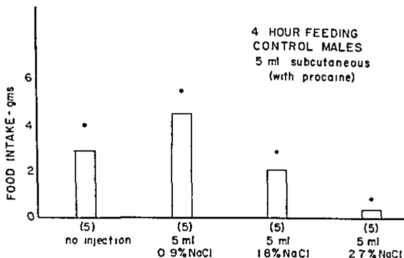


FIGURE 1 Depression of food intake in rats given hypertonic solutions of salt by subcutaneous injection (with procaine to counteract painfulness of injection) From Cort, R L, unpublished

further suggest that the cells which respond to changes in water content in body fluids, the so-called "osmoreceptors," are also involved in [illegible] of feeding. Strominger (1947) had noted that, within limits, the higher water concentration of the diet, the greater the food intake of rats. [illegible] given no water ate little or no dry food, while those given no food drank little or no water. The regulation of food intake appears to be correlated, therefore, with regulation of water exchange. Any explanation of these [illegible] ships should provide for the possibility that there may be within the [illegible] [illegible] capable of acting either [illegible]

[illegible]

important have been included under the appropriate headings in [illegible]

Finally, there is the problem of just what is the animal regulating with reference to food intake? Cowgill (1928), Adolph (1947), and Kennedy [illegible] have assumed that animals in some manner preserve the intake of a [illegible] quantity of energy, a quantity said to equal the total energy expenditure. [illegible] relationship appears to be valid under certain conditions. It does not [illegible] however, when a rat is immobilized for a long time (Ingle, 1949), nor [illegible]

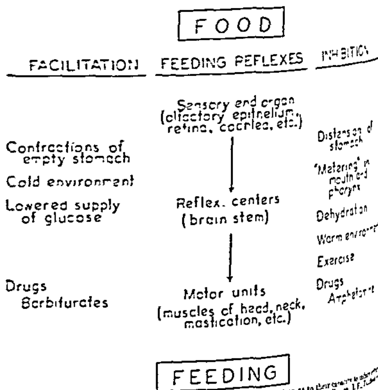


FIGURE 3. Outline of factors affecting food intake, with a suggestion as to their capacity to [illegible] central facilitation or inhibition of feeding reflexes. From Brobeck, J. R. 19[illegible] *In* Fulton, J. F. [illegible] *Physiology*. Saunders & Co., Philadelphia, Pa.

animals are placed in a warm environment where they have difficulty in losing heat. At temperatures slightly above the so-called "neutral" temperature, rats may refuse food completely (Brobeck, 1948), while heat stress has also been observed to inhibit feeding in rabbits (Gasnier and Mayer, 1939), in dairy cattle (Ragsdale *et al*, 1948), and in human infants (Cooke, 1952) Herrington (1940) showed that, at these warmer temperatures, the metabolic rate of rodents is definitely higher than it is at slightly lower temperatures The reduced food intake, therefore, cannot be a result of a lessened need for energy, but [illegible]

their normal caloric intake on the first day following the change Their eating [illegible]

In chronic experiments, they observed a better, though not a perfect, correlation between these two From their data, one may suggest that the amount of food eaten *is determined, first of all, by what happens to the food* This is another way of saying that food intake is conditioned by the state of the intermediary metabolism But the nature of the intermediary metabolism, in turn, is affected by the composition of the diet and the conditions of feeding (Tepperman *et al*, 1943, Lundbaek and Stevenson, 1948) If the pathways of metabolism are not altered when an animal spends a greater amount of energy in activity, a larger amount of food should be required to suppress appetite and initiate satiety, but if the level of metabolism is constant while the composition of the diet is changed, the animal may eat either more or less food than is needed, depending upon whether the new diet intensifies or minimizes the critical changes serving as signals to the nervous system From the acute experi- [illegible]

the metabolism changes and, with this change, the rat now acquires a greater satiety value than it had before It is not necessary to postulate some change in the regulation to account for these observations, and there seems to be no evidence that the regulation *per se* is affected Yet there are ample data to establish the existence of the metabolic changes Hence, when pathways of disposal of food are altered, the amount of food taken may be affected, and the food intake may be regulated at a new level

Finally, as a number of other regulations have been mentioned in this paper, including body temperature, pulmonary ventilation, posture, and others, the author is led to question whether, in studying the control of food intake, effec- [illegible]

an isolated phenomenon, but is an intimate part of the regulation of energy

further suggest that the cells which respond to changes in water concentration in body fluids, the so-called "osmoreceptors," are also involved in regulation of feeding. Strominger (1947) had noted that, within limits, the higher the water concentration of the diet, the greater the food intake of rats. Animals given no water ate little or no dry food, while those given no food drank little or no water. The regulation of food intake appears to be correlated, therefore, with regulation of water exchange. Any explanation of these relationships should provide for the possibility that there may be within the body

have assumed that animals in some manner preserve the intake of a definite quantity of energy, a quantity said to equal the total energy expenditure. This relationship appears to be valid under certain conditions. It does not apply, however, when a rat is immobilized for a long time (Ingle, 1949), nor when

FOOD

FACILITATION	FEEDING REFLEXES	INHIBITION
	Sensory end organ (olfactory epithelium, retina, cochlea, etc.)	
Contractions of empty stomach	↓	Distension of stomach
Cold environment		"Metering" in mouth and pharynx
Lowered supply of glucose	Reflex centers (brain stem)	Dehydration
	↓	Warm environment
		Exercise
Drugs Barbiturates	Motor units (muscles of head, neck, mastication, etc.)	Drugs Amphetamine

FEEDING

FIGURE 2. Outline of factors affecting food intake, with a suggestion as to their capacity to induce either central facilitation or inhibition of feeding reflexes. From Brobeck, J. R. 1955. *In* Fulton, J. F., *Textbook of Physiology*. Saunders & Co., Philadelphia, Pa.

(1940) showed that, at these warmer temperatures, the metabolic rate of rodents is definitely higher than it is at slightly lower temperatures The reduced food intake, therefore, cannot be a result of a lessened need for energy, but must have some other explanation Another circumstance when energy intake does not equal energy expenditure was discovered by Strominger, Brobeck, and Cort (1953) in experiments where the composition of the diet was altered When fat was added to a standard diet, the rats often ingested three times their normal caloric intake on the first day following the change Their eating

In chronic experiments, they observed a better, though not a perfect, correlation between these two. From their data, one may suggest that the amount of food eaten is determined, first of all, by what happens to the food This is

ical changes serving as signals to the nervous system From the acute experi-

evidence that the regulation *per se* is affected Yet there are ample data to establish the existence of the metabolic changes Hence, when pathways of disposal of food are altered, the amount of food taken may be affected, and the food intake may be regulated at a new level

and their actions offer common features. The regulation of food intake is not an isolated phenomenon, but is an intimate part of the regulation of energy

exchange involving heat production and heat loss, the expenditure of energy for muscular activity, and the storage of energy as protein, carbohydrate, and fat. Feeding is likewise closely linked with regulation of water intake and water loss, and these, in turn, are also related to body temperature. The function of the nervous system in these regulations is always an integrating one, in which there may be observed what Adolph (1947) has called "priorities and compromises" The study of appetite and satiety will advance as more is learned about other regulations, at the same time that an understanding of the regulation of feeding behavior may help to clarify other problems. One of the most encouraging results of the conference on which this monograph is based is the evidence presented here that these problems are beginning to claim the interest and the enthusiasm of a talented group of investigators, and that the number of those studying these important mechanisms is steadily increasing.

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THE TIME FACTOR IN THE ADJUSTMENT OF FOOD INTAKE TO VARIED CALORIC REQUIREMENT IN THE DOG. A STUDY OF THE PRECISION OF APPETITE REGULATION*

By Henry D. Janowitz and Franklin Hollander
Gastroenterology Research Laboratory, The Mount Sinai Hospital, New York, N. Y.

The factors that regulate the intake of food in men and animals are incompletely known, in spite of the great precision with which the body adjusts intake to its needs under ordinary physiological conditions The information available at present suggests that many variables are involved, among them environmental temperature, the integrity of several hypothalamic structures, oropharyngeal stimuli, gastrointestinal distention, "emotional" and other conditioned responses, energy requirements, and perhaps circulating metabolites, as well as genetically determined metabolic pathways In the various experimental analyses of these factors already published, an underlying assumption has been that changes in these variables are *promptly* reflected in eating behavior through the regulatory devices concerned with food intake In the study here reported, this presupposition was abandoned, with the thought that complete adjustment might require long periods of time for its attainment [illegible]

[illegible] eff[illegible] ap[illegible]

ing of food into the stomachs of gastrostomized dogs, shortly before they were offered the regular oral meal, depressed oral intake by a corresponding volume, [illegible] imme- [illegible] formed [illegible] rated [illegible] these [illegible] were interpreted as being dependent solely on gastric distention These experiments were later extended by Share, Martyniuk, and Grossman,[2] who also studied the effect of intragastric feeding on oral intake in fistula dogs. They fed 33, 50, 66, or 133 per cent of the voluntary daily caloric intake intragastrically four hours after each regular daily *ad lib.* feeding for three or four weeks. Intragastric feeding of 33 per cent of the caloric requirement had no appreciable effect Larger percentages reduced the amount eaten, but the depression in oral food intake was not fully compensatory; even a level above 100 per cent (133 per cent for one week) did not abolish oral intake completely Both these studies were based on relatively short-term experiments

* This work was carried out with the aid of a grant from the Altman Foundation, New York N Y
A preliminary report of this investigation was presented before the American Physiological Society of Washington, D C at the Federation Meeting held in Chicago, Ill, in 1953 [?]

The present report presents the effect of more prolonged intragastric administration on the intake of food by mouth in fistula dogs, employing periods of about three months each, and three fractions of the average caloric requirement as measured in control experiments In particular, evidence is presented bearing on the rate as well as the precision of adjustment of oral food intake to such variations in caloric requirement

Methods

Three adult female mongrel dogs with simple gastric fistulae were used in this study One fistula was of the Ssbanajew-Franck type,[4] two other dogs were fitted with the metal-plastic cannula described by Thomas[5] The dogs were housed in individual cages and were fed by the same animal attendant throughout the investigation They were allowed to eat *ad lib* once each day, at the same time in the early afternoon Excess amounts of food were offered the dogs in tared pans and were permitted to remain in the cages for exactly 45 minutes, following which the residues were removed and weighed There was free access to water at all times The dogs were weighed once weekly Housing these animals in a constant temperature chamber was not possible, though the desirability of this factor was apparent to us from the onset Observations were not made during the hot summer months The oral foodstuff was invariably a commercial whole dog food (Pard, Swift, regular) One gram of this material is equivalent to 1.2 Cal, and has a volume of 1 ml Its caloric value is derived as follows 38.3 per cent from protein, 23.4 per cent from fat, and 38.3 per cent from carbohydrate The average daily food intake, calculated on a weekly basis, and the related body weight were considered to be stabilized when successive values over a period of weeks no longer showed well-defined trends by graphic inspection This time interval was designated Period I

When the average daily food intake and the weekly body weight became stabilized, a predetermined fraction (50, 100, or 175 per cent) of this mean voluntary caloric intake (control value) was supplied each animal daily by intragastric instillation This procedure was followed for a period of 14 or more weeks—designated Period II—for each fraction and for each dog The foodstuff used for this purpose was a complete semipurified aliment suspended in water (Pregestal), previously devised in this laboratory for human tube feeding This aliment was used in place of Pard for two reasons (1) the large quantities of solid, prepared dog food could not easily be administered intragastrically, and (2) in the 175 per cent experiments, the volume would have been nearly twice that of the control volume The calories supplied by the intragastric feeding were derived as follows from protein 25 per cent, fat 16 per cent, carbohydrate 59 per cent The caloric density of the intragastric material was adjusted by addition of water, so that the volume placed in the stomach equaled the daily volume of food eaten voluntarily by each animal during the control period Such an intragastric feeding during the experimental periods was given six hours before each oral feeding, in order to insure complete gastric emptying before oral ingestion was permitted

EFFECT OF INTRAGASTRIC FEEDING
OF 50% OF CALCULATED CALORIC REQUIREMENTS ON ORAL FOOD INTAKE
Dog #248

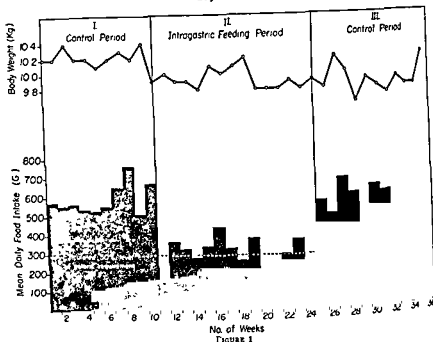


FIGURE 1

Period III followed directly after Period II and was characterized by ces sation of intragastric alimentation and a return to the experimental condition of the first period Its duration will be described below. In several instance Period III was considerably prolonged, for reasons to be discussed later. Suc prolongations are designated III* (see TABLE 1).

Results

A The control period Oral intake during Period I did not reach a plate indicative of relative stability of the desire to eat until 24, 23, and 15 wee (for the three dogs respectively) had elapsed after starting the experimen When such a level was finally reached and maintained for 10 weeks, the bo weight also manifested stability in even greater degree Thus, σ_B† for bo weight never exceeded ±0 2 kg (3 per cent of the corresponding mean) where σ_O for oral intake rose as high as ±96 gm. (15 per cent of its correspondi mean), see TABLE 1

... The eff ... similar in ... at the th

† In conformity with current usage, σ_x is used to represent the standard deviation of the distribution of variate x, and $\sigma_{\bar{x}}$ that of its mean.

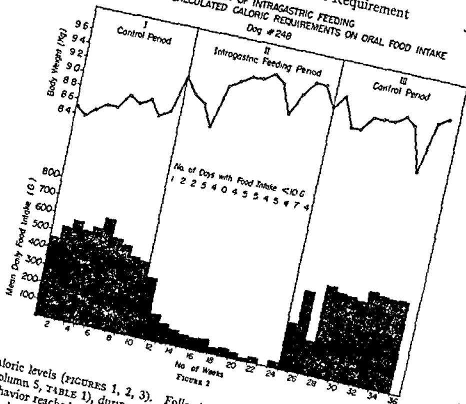


FIGURE 2

caloric levels (FIGURES 1, 2, 3). Following a transitional adjustment period (column 5, TABLE 1), during which oral intake decreased progressively, eating behavior reached a new plateau (column 6), again indicative of a stability of the desire to eat. By this criterion, eating was readjusted with considerable precision to attain complete compensation of caloric supply. During the 50 per cent level experiments, the mean daily food intake by mouth slightly exceeded the mean daily deficit in calories given by fistula, but this difference was not significant statistically at the 1 per cent level of probability. During the 100 per cent level experiments, oral food intake was suppressed almost but not completely, here again the average amount eaten in each case was statistically not significant. (Note that for dog No. 245, $p = 0.014$, which—though greater than 1 per cent—may be considered to betoken uncertain significance.) During the 175 per cent level experiments, oral food intake was virtually abolished when equilibrium was achieved. On the average, one dog continued to eat 34 gm a day and the others took 11 and 10 gm respectively, but none of these values is significant. For the statistical data on which these judgments are based, see TABLE 2. In spite of these conclusions regarding the

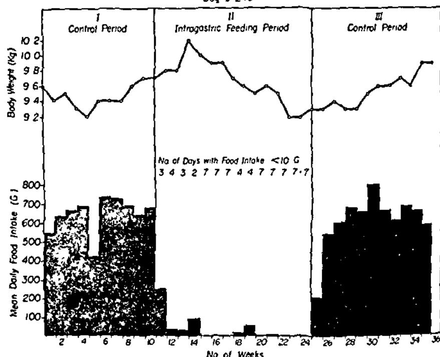


FIGURE 3

absence of statistical significance, it may well be that the persistence of a small residue of eating behavior above the expected in every one of the nine experiments does have some physiological significance, because of its universal occurrence

It is noteworthy also that, in the 100 per cent and 175 per cent experiments, when oral food intake was virtually abolished by intragastric feeding, the dogs would sniff at the food offered them daily, often take one or two mouthfuls,

TABLE 1

EFFECT OF INTRAGASTRIC FEEDING ON ORAL FOOD INTAKE

	Dog No	Period I Control			Period II Intragastric Feeding				Period III Postintragastric Feeding			
		Time (wks)	O ± σO	B ± σB	Ad just Period (wks)	Equil Period (wks)	O ± σO	B ± σB	Ad-Just Period (wks)	Equil Period (wks)	O ± σO	B ± σB
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
A—50% Experiments	245	10	602 ± 82	10.0 ± 0.1	3	11	348 ± 79	10.3 ± 0.2	2	9	393 ± 75	10.6 ± 0.1
									*11**	*13*	*542 ± 70*	*10.8 ± 0.3*
	246	10	402 ± 51	7.9 ± 0.2	6	8	212 ± 42	8.0 ± 0.1	5	9	390 ± 57	8.0 ± 0.1
	248	10	586 ± 71	10.2 ± 0.1	2	12	312 ± 57	9.9 ± 0.1	3	12	570 ± 84	9.9 ± 0.2
B—100% Experiments	245	10	594 ± 96	10.0 ± 0.2	4	10	90 ± 27	10.3 ± 0.3	4	10	495 ± 29	10.0 ± 0.4
									14*	10	553 ± 44	10.0 ± 0.1
	246	10	468 ± 76	7.5 ± 0.2	4	10	45 ± 27	8.5 ± 0.2	3	11	345 ± 34	8.1 ± 0.2
									14*	10	447 ± 25	7.7 ± 0.1
	248	10	526 ± 51	8.6 ± 0.1	7	7	30 ± 14	9.3 ± 0.2	3	11	510 ± 44	9.2 ± 0.2
C—175% Experiments	245	10	552 ± 44	10.0 ± 0.1	4	10	34 ± 75	10.5 ± 0.1	4	12	539 ± 60	10.2 ± 0.1
	246	10	447 ± 25	7.7 ± 0.1	6	8	11 ± 20	8.0 ± 0.2	4	12	433 ± 51	8.1 ± 0.2
	248	10	647 ± 90	9.5 ± 0.1	4	10	10 ± 17	9.6 ± 0.3	4	12	669 ± 71	9.8 ± 0.2

$O \pm \sigma_O$ Mean food intake in grams ± the standard deviation of the distribution
$B \pm \sigma_B$ Mean body weight in kilograms ± the standard deviation of the distribution

* The 9 sets of data in period III (columns 9–12) which are not marked by an asterisk correspond to the first reattainment of a stabilised oral intake following cessation of intragastric feeding. Six of these O values are statistically identical with the corresponding control values (column 3). In the other 3 cases, measurement of O values for an additional period (designated III*) yielded new equilibrium values, marked by an asterisk, which are also in agreement with the control values. For the pertinent statistical test data, see TABLE 3

TABLE 2

TESTS OF SIGNIFICANCE OF DIFFERENCES BETWEEN OBSERVED (O) AND EXPECTED (E) EQUILIBRIUM VALUES FOR MEAN ORAL FOOD INTAKE IN PERIOD II

	Dog No	$O \pm \sigma_O$	$E \pm \sigma_E$	O − E	n	t	p
A—50% Experiments	245	348 ± 79	301 ± 82	47	19	1.3	0.20
	246	212 ± 42	201 ± 51	11	16	0.5	0.62
	248	312 ± 57	293 ± 71	19	20	0.6	0.55
B—100% Experiments	245	90 ± 27	0 ± 96	90	18	2.7	0.014
	246	45 ± 27	0 ± 76	45	18	1.7	0.10
	248	30 ± 14	0 ± 51	30	15	1.7	0.11
C—175% Experiments	245	34 ± 75	0 ± 44	34	18	1.6	0.13
	246	11 ± 20	0 ± 25	11	16	1.0	0.32
	248	10 ± 17	0 ± 90	10	18	0.3	0.75

These t-tests were set up on the hypothesis that an observed mean oral intake (O) with variance (σ_O^2) is not [illegible]

cent level of probability In the case of dog No. 245 in the 100 per cent experiment, p = 0.012, which is so close to 1 per cent that it also may be considered to indicate significance of the difference. Because of the failure of three of the nine equilibrium levels in Period III to agree with the corresponding values in Period I, measurement of oral intake was continued for another two and one-half or three months—designated Period III* (TABLE 1). In all three cases, these mean equilibrium values measured in Period III* were now found to differ from those in Period I by amounts which are not significant at the 1 per cent level of probability. Thus, if we choose to define the state of equilibrium attained after cessation of fistula feeding in terms of a quantitative return to the control level of food intake established during the initial control period, such a state was attained in all nine cases—either in Period III or in Period III*—but if we choose to define it in terms of stability of intake regardless of magnitude, then this state was established in six of the nine cases.

C *Rate of adjustment.* The transition from the equilibrium value for oral intake in Period I to that in Period II started immediately, during the first week of intragastric feeding, but complete readjustment required an average of 4.4 weeks Thus, in the 50 per cent experiments (column 5, TABLE 1), the transition period lasted 3, 6, and 2 weeks for the several dogs respectively, for the 100 per cent level, 4, 4, and 7 weeks; and for the 175 per cent level, 4, 6, and 4 weeks.

The increase in oral food intake which followed the cessation of intragastric feeding (i.e., during the transition from Periods II to III) was likewise progressive, requiring an average of 3.6 weeks for reattainment of a plateau value. For the individual dogs (column 9, TABLE 1) the times were 2, 5, and 3 weeks in the 50 per cent experiments, 4, 3, and 3 in the 100 per cent group; and 4, 4, and 4 in the 175 per cent group of experiments When the return to equi-

TABLE 3

TESTS OF SIGNIFICANCE OF DIFFERENCES BETWEEN EQUILIBRIUM VALUES FOR MEAN ORAL FOOD INTAKE (ΔO) IN PERIODS I AND III, ALSO FOR MEAN BODY WEIGHT (ΔW)

	Dog No	ΔO	n	t	p†	ΔW	n	t	p†
A—50% Experiments	245	209	17	5 3	0 0001	0 6	17	3 1	0 006
		60*	21	1 8	0 09	0 8*	By inspection		<0 01
	246	12	By inspection		>0 01	0 1	By inspection		>0 01
	248	16	By inspection		>0 01	0 3	20	0 8	0 45
B—100% Experiments	245	99	18	2 8	0 012	0	By inspection		>0 01
		41*	18	1 1	0 27	0*	By inspection		>0 01
	246	123	By inspection		<0 01	0 6	19	6 7	0 0001
		21*	By inspection		>0 01	0 2*	By inspection		>0 01
	248	16	By inspection		>0 01	0 6	19	6 4	0 0001
C—175% Experiments	245	13	By inspection		>0 01	0 2	By inspection		>0 01
	246	14	By inspection		>0 01	0 4	20	5 7	0 0001
	248	22	By inspection		>0 01	0 3	By inspection		>0 01

* These values for ΔO and ΔW correspond to period III* (see footnote to TABLE 1)
† ΔO and ΔW are significant by the t test when $p \leq 0\ 01$, n = degrees of freedom

ibrium of eating behavior was defined in terms of a quantitative return to the control level (in Period III*) rather than stability of intake (in Period III), the mean transition time was longer (6 9 weeks).

D Maintenance of constancy of body weight During the period of intragastric feeding, body weight was maintained at statistically constant levels in the 50 per cent experiments, at the 100 per cent level in one of the three, and *in the 175 per cent experiments in two of the three (column 8,* TABLE *1).* Fol-

(column 12, TABLE 1). Statistical significance was measured by the t-test, using a 1 per cent probability level as criterion (TABLE 3).

Discussion

The two interrelated aspects of these results on caloric adjustment, *i e*, its precision and its rate, require discussion In evaluating the precision of such adjustment to varied needs, one must take into account the considerable range of variation of the data during the control periods Whereas body weight was maintained within rather narrow limits, the weekly averages for daily food intake had wide ranges of variation Adjustment of caloric intake to diminished or augmented caloric need—when such requirement was offset, in part or in whole, by direct instillation of food into the stomach—was made by each

completely for the magnitude of this difference, as judged by accepted statistical criteria Although considerable time was required for the regulatory mecha-

nisms to achieve a new equilibrium, there can be no doubt that these mechanisms are capable of fine adjustments of caloric intake to the residual caloric requirement The precision of caloric adjustment is also illustrated by the return to control food intake values when intragastric feeding was stopped When a stabilized level of food intake was again achieved, a statistically significant difference in oral food intake between the pregastric and postgrastric feeding periods was present in none of the nine experiments This precision is also reflected in the fact that, during the intragastric feeding experiment at the 50 per cent level, no significant rise in body weight occurred during the period of equilibrium This was not the case in the 100 per cent experiments, where a rise in body weight occurred in two of the three experiments. This increase may be expected, since caloric intake during the transition period was greatly in excess of need, and this excess could not be compensated for during the period of equilibrium During the 175 per cent experiment, a rise in body weight was to be expected, but the actual increase was surprisingly small. This kind of finding is not easily explained, but it has been observed by others as well[illegible] Gross loss of nutrient material from the intestinal tract by diarrhea did not occur

To what stimulus or stimuli was the organism responding during these experiments? The factors mentioned in the introduction to this report do not seem to be involved Oropharnygeal cues were eliminated, although they play a role ordinarily in the "metering" of food intake The gastric distention factor, demonstrated in previously published studies, remained constant in the present experiments and thus cannot account for the variation in intake in response to variations in intragastric supply. Environmental temperature was not rigidly controlled in our experimental setup, although the need for such control was appreciated, and our results might well have been more elegant if external temperature had been completely controlled. There is no reason to suppose, however, that total energy requirements were systematically altered in any considerable degree by this or any other environmental condition.

These experiments suggest that some systemic factor, a metabolic one, was influencing the integrative activity of the central nervous system, especially of those areas of the hypothalamus shown by Brobeck and his co-workers to be involved in the physiological regulation of food intake. There is no completely convincing [illegible] any known inter[illegible]gulation At the [illegible]e been stimuli in [illegible] were effective is completely obscure Strominger and Brobeck[8] have rejected the caloric content of food *per se* as the "intrinsic food factor" which signals to the animal to stop eating [illegible]ments in [illegible] n slowly [illegible] Aside [illegible] the ca[illegible] [illegible]r factor, [illegible]nce oral

ingestion continued in spite of the complete satisfaction of actual caloric nee albeit in gradually decreasing amounts Brobeck and Strominger's suggestion that the stimulus may be the specific dynamic action (S D A) of the food mixture ingested rather than its caloric content *per se*, is of great interest and merits consideration in this connection. However, some preliminary calculations—using data from our 50 per cent and 100 per cent experiments and these authors' assumptions regarding the S D A of mixed diets—afford no evidence that constancy of S D A per day was achieved by these animals

Equal in interest to the precision with which caloric adjustments were made by these dogs under conditions of varied caloric supply by fistula is the finding that a significant time factor is involved in the attainment of complete adjustment The adjustment was begun promptly after each variation in intragastric supply, but it was completed very slowly Four to seven weeks were required for achieving equilibrium in two-thirds of all the experiments in Periods II and III, and even longer if we consider Period III* Fragmentary indications of the importance of this time "lag" already exist in the literature Strominger, Brobeck, and Cort[7] noted that caloric adjustment to a diet of high aloric density, high in fat and suboptimum in protein, required four to five ays in slowly growing rats Cowgill[5] has described caloric adjustments occur-ng over an eight-day period in mature dogs when the caloric density of the *ad lib* diet was altered Some previous experiments of Janowitz and Grossman[8] on the effects of variations in nutritive density, achieved mainly by dilution with noncaloric materials, on food intake in dogs, also indicated that considerable time was required for the achievement of adjustment The present studies demonstrate convincingly the magnitude of this time interval

Speculations regarding the nature of the systemic factors influencing integrative regulation of food intake must take into account these slow rates of adjustment, as well as the precision of that integration It seems unlikely to us that this is accomplished under the influence of a single intermediate metabolite Rather, the time curves of our experiments suggest the influence of at least two different major mechanisms operating through a common regulating center The precision of adjustment in the present experiments may be taken to indicate the functioning of a *metabolic* mechanism sensitive to variations in caloric requirements The time required to complete these precise adjustments, however, suggests the progressively diminishing operation of another mechanism which tends to maintain the act of eating, apart from nutritional need This second device may be conceived of as a wholly neural component of the regulatory mechanism The long duration of this readjustment period following an increase, as well as a decrease, in caloric need suggests the existence of considerable "inertia" in this second device

The presence of this latter system or mechanism is supported by these results iewed from another angle From a statistical point of view, the amount of ood eaten by each animal during the period of intragastric feeding is *exactly* ompensatory, when the range of variation of control values is taken into count, *i e*, when the data are evaluated in routine statistical fashion In ery one of the experiments, however, the animals ate a clearly measurable

of food over that expected from their residual caloric needs These
cent levels, but even
nts when intragastric
feeding greatly exceeded the actual control values. This persistent ingestion of small amounts of food despite caloric surpluses may indicate some limited persistence of the operation of the second regulatory mechanism just mentioned Scattered evidence for the existence of such a device may perhaps be found also in ... food deficits ... caloric adjustment in Brobeck's experiments with rats ... nding also may be taken as evidence in support of such a mechanism. This drive to eat, independent of caloric needs, was also encountered in the work on the human subject, Eddie, reported by one of us in the present conference.[11] Here too, eating (sham-feeding) continued in great amounts in spite of the fact that the caloric need of the subject was clearly being met by intrajejunal alimentation.

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the realm of pure speculation at present.

This study is subtitled "A Study of the Precision of Appetite Regulation," and the word "appetite" has yet to appear in this discussion. Some years ago, Janowitz and Grossman[12] proposed a rather simple definition of "appetite," which may be considered in the present context. They defined appetite as the desire to eat, and suggested that, operationally, it can be measured in animals in terms of the amount of food eaten. In this light, the problem of ... In
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gree of precision by the calories required to maintain equilibrium In addition to this finding, however, appetite and the amount of food ingested by mouth can be independent of caloric need, though to a variable extent, by reason of the second regulatory mechanism.

Summary

The effects of variation in caloric requirement on oral food intake were investigated in gastric fistula dogs. Under relatively stabilized conditions, fractions of the average caloric needs, as determined during appropriate control periods, were directly instilled into the stomachs of these dogs, and the effects on *ad lib* oral food intake observed. When 50, 100, and 175 per cent of the caloric requirements ... food intake
was almost complete
tive excess of food
cision of caloric intake to residual caloric need, required long periods of time (weeks) to be accomplished, both during and following the periods of intra-

gastric feeding. These results are tentatively interpreted as indicating the existence of two regulatory mechanisms: the one a homeostatic metabolic device for insuring adequate caloric intake under conditions of varying need; and the second, a wholly neural mechanism tending to maintain the act of ingestion regardless of caloric need.

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ROLE OF THE EMOTIONS IN HUNGER AND APPETITE

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The role of emotions in relation to food can hardly be overrated What we eat, when we eat, and how we eat, is determined in innumerable ways, not alone by nutritional needs, but also by social and national traditions, moral commands and restrictions, and individual psychologic experiences Emotional aspects of eating pervade our life to such an extent that they are taken [illegible]

The Thanksgiving holiday may serve as an illustration of the many ways in which food and emotions are interrelated There is every reason to doubt that the sudden desire for turkey which overcomes the people of the United States on that day is related to a physiologic need, or to a deficiency not noticeable during the rest of the year Yet those who must go without turkey and all the traditional trimmings will feel unjustly treated, dissatisfied, and left out. The feeling that every American is entitled to his Thanksgiving turkey is officially recognized and the Armed Forces, and other large institutions supply this viand Turkey contains no special morale-building vitamin, mineral, or other secret ingredient Its effect is due to what it stands for, a symbol of home, family, and congenial and abundant living.

Few will pause to remember that Thanksgiving was first celebrated in gratitude for an ample harvest which guaranteed survival during the coming winter. Thus, the holiday indicates the deep-seated fear of famine that haunted early settlers in New England.

I shall resist the temptation to cite other examples of the innumerable ways in which food is used in different religious practices, rituals, and taboos and in accordance with national and social traditions. I am sure that everyone has made many observations in this connection that readily come to mind

The emotional aspects of eating are related to two basic facts: first, the universal fear of starv[illegible] early lif[illegible] ther pe[illegible] -mo- tic[illegible] imi- tive relationship between the discomfort of hunger and the pleasure of its satisfaction becomes exceedingly complex through these modifying emotional influences. There has been much concern about the indefiniteness of the terms hunger and appetite It seems to me that this problem is not a semantic one, but that it is related to the fact that, for each individual, the physiologic and psychologic experiences are so closely interwoven.

For research purposes, it may be desirable to come to clearer definitions and

concepts of the terms, and I feel in agreement with such efforts. In clinical work, however, it is difficult to make this differentiation, except for extreme situations. Actually *hunger* and *appetite* are not sufficient to describe the various sensations which different individuals experience in their demand for food. There are many conditions in which terms such as yearning, craving, addiction, or compulsion are more descriptive of the psychological state.

In view of the extraordinary importance of food in human life, it is astounding how little systematic attention has been paid to the psychological aspects of eating.

The British novelist, E. M. Forster, points out in his essays on *Aspects of the Novel* (1927) that eating is a human activity which literature has shamefully neglected in favor of love. "Food in fiction is mainly social. It draws characters together, but they seldom require it physiologically, seldom enjoy it, and never digest it unless specially asked to do so. They hunger for each other, as we do in life, but our equally constant longing for breakfast and lunch does not get reflected."

De Castro,[1] in *Geography of Hunger*, speaks of the "taboo of hunger." He tries to explain what he calls the "conspiracy of silence" about hunger and its motivating force in human behavior as due to the prejudices of the Western World, where only reason had social value and instincts were considered expressions of the lower animal nature.

When Freud broke through this taboo on instincts, he and the psychoanalysts after him concentrated on the variations and vicissitudes of the sexual instinct. This focus is so exclusive that abnormal food attitudes have been explained in terms of deviations of the psychosexual development.

The late Ralph Linton[2] expressed the opinion that this one-sidedness should be understood in social terms. To the upper and middle classes of the late Victorian and pre-World War I era (on whom the early psychoanalytic observations were made), the idea of hunger and deprivation was so foreign that sex had become the basic drive in which difficulties were experienced and expressed. It is becoming apparent now that there is need to consider the drive for food as of psychological significance in its own right, although its variations and interaction with other vital experiences, including sexual development, are endless.

The events of the last two decades, the terror of concentration camps, and the systematic starvation of European countries during World War II exposed the cultured, scientifically, and psychologically oriented Western World to the horror and devastation of hunger as a human experience. Hunger there had been through the ages, but it belonged to the distant past or was considered the suffering of the multitudes in underprivileged countries.

One of the oldest authentic records of history, *The Stele of Famine*, found in the First Cataract of the Nile, tells of the misfortune of crop failure and the deterioration of human behavior during famine. "Each man has become a thief to his neighbor." Recent observations in concentration camps and reports by survivors tell the same tale: how the hunger drive is completely overpowering, sparing nothing and no one, and inciting every kind of baseness in human behavior.[3]

Realizing our ignorance of starvation and its consequences, Keys, in collaboration with other research workers during the war years, studied experimental starvation in a group of healthy young men. The monumental report[4] of their own findings includes also a review of the documents of starvation in historical times, of the experiences of explorers, and recent wartime observations.

The outstanding impression is that of the extraordinary similarity of the reactions to hunger of all human beings, regardless of time and place, indicating the deep biological source of psychological changes. There have been few exceptions where individuals with high motivation and spiritual strength have risen above the brutal debasement by hunger, though there has been no escape from the suffering.

Two phases stand out in the course of starvation: an immediate reaction to being deprived of food, and a final picture, when undernutrition has become extreme

In the early phase, there is a relentless preoccupation with food, a coarsening of all other emotional responses, increasing selfishness with complete loss of other human considerations, and loss of sexual desire. In the final stage, the picture is dominated by apathy and withdrawal from life, by heightened irritability over any disturbance. During recovery, the urge for food seems to be insatiable, and preoccupation with food and a fear of not getting enough persist long after the body has made a physiological recovery.

In our contemporary life, such extremes of food deprivation occur only under exceptional circumstances People may react to sudden dietary restrictions with fear of starvation Meerloo,[6] who has been exposed to life in a concentration camp, has described how patients who, while undergoing surgery, are given a very limited amount of food or no food at all may react in a way that closely resembles the behavior of people in the last stage of starvation. He raises the question whether "the lack of the will to live" may not be a result of this deprivation. For the restoration of such patients, indulgent treatment, including careful feeding, is indicated

Even in less drastic situations, fear of starvation and anxiety about loss of body substance may be aroused I have become impressed by the frequency with which fat patients, long before any significant loss of body weight has [illegible]

tion of the exaggerated role that food plays in the adjustment of these people to life

The case of a young woman may serve as an example of this tendency. During a brief interruption of her analytic treatment, she began, on her own decision, a reducing regime After two weeks, when she had lost approximately 10 pounds, she was in a state of extreme tension She was still very much overweight. She described an insane desire for all kinds of food, even those she ordinarily loathed, and the thought of food kept her awake. She was tired and dizzy during the day and her knees felt weak. She felt as if she had to watch every step, in a physical sense, as well as in regard to eating "There's a feeling of walking right off the edge of something—a feeling of no volition"

She consumed large quantities of tea, smoked continuously, tried escape by reading magazines or going to the movies, and she talked to herself in an indulgent voice. Since she wanted to lose weight and wanted to continue the diet, she would tell herself to stay on it: "A command is a command, no matter where it comes from."

The result of this struggle against her active desire for food was a complete disintegration of her usual activities. She finally went off the diet, because she felt "face to face with the 'unhuman' part of myself."

One may raise the question whether this young woman suffered from "fear of starvation," or whether the acute symptoms were a secondary reaction to the changed psychological pattern when she stopped using food to appease emotional needs. There had been many situations in the course of her analysis in which she had described, in great detail, the ups and downs of her emotional reactions. As a matter of fact, she was unusually articulate. She felt that this experience was something outside her other emotional reactions, as indicated by her speaking of the "unhuman" part of herself. On the other hand, the similarity to the behavior described for true starvation is striking.

This episode occurred at a time when the emotional conflicts of her life were far from solved, when, in particular, she had not yet gained insight into the meaning of the excessive desire for food that had dominated her life and had caused the obesity. As she progressed in psychological understanding, she gradually reduced her food intake without suffering from such acute symptoms.

This change in her reaction is of significance for an understanding of the interrelationship between physiological regulatory mechanisms and psychological awareness of these changes. Her weight curve was typical for obese patients with emotional problems. Periods of rapid increase in weight, the active phase of obesity, during which she gained as much as 30 to 40 pounds within five or six months, had alternated with frantic efforts at reducing, always short-lived, and periods of relative weight stability. Altogether she had gained 80 pounds during the six years preceding analytic treatment.

There is every reason to assume that her physiologic regulatory mechanisms were disturbed during the period of rapid gain, or even during the seeming weight stability. Unfortunately, no observations on her glucose utilization were made, and I offer this explanation more as an analogy. She had described her attitude toward her own impulses as "having desire and not being able to appease it—that was always the most horrible thing in the world. As soon as the desire is felt—I have got to satisfy it. I just don't know what abstinence is." For a long time, whatever the desire was, it was experienced as the desire for food which led to overeating and increasing obesity.

As her insight into her psychological problems increased, this tendency changed, even though she continued to be unable to postpone her impulses. "I know I'm voracious in all kinds of things, but now I get the same relief or enjoyment from different things. Formerly there was no choice. I just had to eat. Now I'm still insatiable and I want enormous amounts from whatever it is. But now I can choose and, when I feel this way, I can go to a good movie or well-stacked library, or I might go to a bakery shop and eat my fill, or I may go to bed with a man and enjoy that too. I get the same kind of libidinous

pleasure out of all these different things, the same type of excitement and relaxation" Only after she learned to tolerate the frustration of postponing a felt need, was she able to change her neurotic eating pattern and to approach the stresses and problems of life in a more mature way.

One wonders whether, in such a case, the assumed underlying metabolic disturbances are corrected as the emotional tensions decrease, or whether it is the increased ability to tolerate changes in the homeostatic mechanism that accounts for changes in the eating pattern

I have cited this example to illustrate the fact that the psychological aspects of food intake, arising from the fear of starvation and the interpersonal meaning of food, are closely interwoven. Bettelheim[6] observed in emotionally disturbed children that one of the most deep-rooted fears in all of them was the fear of having to go hungry. Even children who had always had ample food would unconsciously equate disapproval with the threat of being deprived of food By the same token [illegible] the first line of contact with some person in the new environment.

Recognition of the psychological reaction to food deprivation or to mere changes in the esta[illegible] to the clinician who uses [illegible] into a moral issue Consideration of the psychological factors is of importance, both for the success of the medical management, and for the emotional wellbeing of the patient

In a group of diabetic children, it could be demonstrated that the ability to follow the medical regime was directly related to the emotional acceptance of the child and of his illness by the parents[7] [illegible] fact that she had never been properly regulated. Formerly, she had enjoyed a good appetite, but her attitude towards food had changed She said "I may have a feeling of being hungry in the stomach, nevertheless there is no appetite. I know that I must eat, but at the same time I feel I don't want to" She repressed the need for food, although she knew that she would feel better after eating

Psychological considerations are of particular importance in the treatment of old people [illegible] pressure may be achieved, but often at the price of apathy or acute depression

Intricate problems may arise in the treatment of food allergies Such diffi-

culties have been reviewed by Kaufman,[8] who gives a vivid account of the many psychological problems involved in detecting and removing injurious food.

My own observations have been made chiefly, though not exclusively, on obese people. Here, too, we find an interaction of the fear of starvation with individual emotional reactions, as was illustrated in the brief case abstract. The fear of starvation usually does not become apparent until dietary restrictions are imposed. In analysis, however, fear of starvation can be recognized even during the progressive stage of obesity. Overeating for such extremely insecure individuals serves as a double or triple guarantee against the danger of going hungry.

A 12-year-old boy, weighing more than 200 lbs, explained his incessant need for food by his fear of not being strong enough. He had the image that his body was like a sack filled with a kind of blubber. It was his job to keep the sack well-stuffed, otherwise he would become weak and just shrivel up. When he was quite young, he had seen pictures of starved people and had been deeply impressed by their appearance, "as if the stuff had just run out."

More apparent in the obese is the use, or misuse, of food for the expression of emotional conflicts and for the relief of tension and anxieties. This tendency has been the object of detailed studies.[9] Any type of emotional problem may be expressed or acted out through overeating: demand for love and affection or defiant hostility and vain declarations of independence, helpless submission to the world or megalomanic dreams of limitless power, childish indulgence of every whim or destructive self-contempt.

Many shadings of the emotional importance of overeating can often be traced to childhood experiences. As stated before, the indefinite variety of nonnutritional uses of food is related to the fact that the feeding situation is the earliest interpersonal experience. In order to understand the full meaning of this relationship, it is important to recognize that the gratification which the mother feels for being able to appease her child's hunger is emotionally as important as the child's experience of satiation. Thus, this earliest experience is a true symbiosis between mother and child in which each gives satisfaction to the other and also receives it.

Under fortunate circumstances, the range of mutually satisfying experiences increases with the age of the child. The mother takes pride in his genuine growth, and the child will develop many new ways of feeling satisfied and adequate. Eating then takes its proper place as just *one* necessary and enjoyable ingredient of living.

If the mother is insecure, the feeding situation may become overcharged with emotional significance, because the mother needs the gratification of doing something good for her child. Other aspects of the child's development will be inhibited. There are many families where food remains, or becomes, at periods of stress, the only meaningful emotional contact.

The mother of a 16-year-old fat girl described this feeling as follows: "She enjoys me as a mother only when I feed her, prepare food for her, plan menus, or go shopping with her." Tempting her daughter with rich dishes had remained important to the mother, although she complained bitterly about her

greed and embarrassing appearance. Yet to see the girl's face light up when food came into the picture reassured her that she had not completely failed as a mother

The feeling that "Everything I did was wrong" appears as a monotonous refrain in the accounts mothers give of their efforts on behalf of a fat son or daughter Usually, by the time of adolescence, there is little left of mutual enjoyment, and everything seems to center around the struggle of keeping the fat youngster on a diet These efforts are doomed to failure, because food is the only means by which such an adolescent can hold in check his ever-increasing anxiety about being hopeless and inadequate.

Seen from the child's point of view, the overintense but precarious relationship with his mother (occasionally a father may play the dominant role) imbues him with a sense of his helplessness but, also, with a feeling of his obligation to [illegible]

Only a spectacular success, achieved without visible effort and tedious work, will be evidence of his greatness The contrast between the quiet, even withdrawn behavior and the magnificence and violence of the daydreams is tremendous

There is such a discrepancy between what a fat person wants to achieve and what he can and does achieve, that repeated defeats and disappointments are unavoidable Excessive eating does not compensate for the failure, but it gives a semblance of satisfaction and relieves tension.

Obesity is such a severe social handicap that failures are apt to be explained as due to it. Frantic efforts at reducing are undertaken in the hope of achieving unrealistic goals Usually, such efforts are short-lived and are followed by renewed gain in weight Sometimes, when the expected rewards are not forthcoming after the weight has gone down to normal, the downhill course may continue, resulting in anorexia nervosa

I wish to quote from the history of a young woman who, when she was 14, was made to feel that her obesity was the cause of her troubles, that it was a visible sign of her not being "good enough." She began to reduce but, after she had become slim, she still felt she was not "right," because now her family wanted her to wear more sophisticated clothes She was disappointed over not getting the desired approval, and went on a real starvation program with the explanation: "I am not worthy, I do not deserve to eat."

When I saw her, she was in a miserable general condition, her weight being just above 70 pounds There was extreme fatigue and loss of interest in food, and a fear of feeling too full when she ate

For a long time, there had been no loss of appetite In spite of her noneating, she suffered from feeling hungry but denied herself food with the self-belittling explanation: "I do not deserve it" Only when her condition had become extremely poor was there a genuine lack of interest in food. She was so run down that she could eat only when she was relaxed, not tired and tense, and did not need to make any effort to get food This condition added to her self-

depreciation because it "proved" that she was "spoiled." Her symptoms showed similarity to the behavior of people in the late stage of starvation, who no longer go after food. In this girl, the psychological reaction did not improve until the worst effects of the malnutrition had been corrected.

In discussing the emotional aspects of eating, I have attempted to show that physiologic factors influence the emotional well-being, and that psychologic experiences may change eating patterns. Both factors are often closely associated. I have focused my remarks on the developmental background of this interrelationship.

By implication, I have expressed the concept that hunger and appetite are phenomena which the biologist studies and clarifies according to physiologic pathways and regulatory mechanisms, and which the psychiatrist tries to understand as manifestations of behavior and feelings. Though their methods differ, it should be apparent that, basically, both the biologist and the psychiatrist are dealing with the same human experience.

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Discussion of the Paper

Doctor Leon Moses (*College of Physicians and Surgeons, Columbia University, New York, N Y*). I should like to ask a psychological question. What evidence is there that the preoccupation with food of patients who have had no previous experience of food deprivation or starvation and are undergoing dietary restriction is actually due to an unconscious fear of starvation?

I question that fear of starvation is a primary unconscious motivational mechanism in individuals who have had no traumatic starvation experience. It appears more probable that the excessive conscious and unconscious food thoughts, fantasies, and preoccupations of patients undergoing weight reduction constitute, rather, a fear of the loss of excessive eating for its various psychic functions. Patients fear to give up compulsive eating because of its tension-relieving function, its oral pleasure gratification, and their need to maintain the "obese facade" as a protective defense against the unrealistic fears of adult life (social, sexual, and competitive relationships). It is this fear which appears to mobilize the unconscious feeding impulses and fantasies.

INTEGRATION OF CURRENT VIEWS ON THE REGULATION OF HUNGER AND APPETITE

By Morton I. Grossman

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Professor E. F. Adolph[1] has said: "Regulations in organisms are mainte-
nances of relative constancie
tained relatively constant"
submit that it is mainly the body's content of nutrients Under special circumstances, regulation of other factors, such as body-heat content or body-water content, may take precedence but, normally, it is probably nutrient stores that are being conserved. Although all classes of nutrients are involved in this regulatory process, for the present discussion we shall confine our considerations to the energy-yielding nutrients; that is, we shall be concerned with calorie balance.

The store of energy in the healthy adult animal body remains relatively constant over long periods It follows that the rates of energy intake and expenditure are essentially equal. The regulatory process which tends to keep them equal involves psychic phenomena, hunger, and appetite. Our interest in these psychic phenomena is from the point of view of how they are related to this regulatory process

We are dealing, then, with the psychic adjuncts of a physiological regulatory mechanism and are at once beset with the problem of whether these psychic states are an overflow into consciousness of an essentially automatic bodily process or are indispensable in the regulatory mechanism. In other words, "To what extent are hunger and appetite merely an awareness that the regulatory process is operating, and to what extent do they participate in the regulation?"

Here, a useful analogy might be drawn between hunger and pain Stimuli which damage or threaten damage to tissue evoke pain. These same stimuli elicit imperative protective reflexes (*e g.* withdrawal), and these stimuli continue to occur even when the pathways from the spinal cord to the brain no longer are intact, thus preventing pain perception.[39] Perhaps a better example comes from respiratory physiology. Here a single word, dyspnea, refers both to a sensation and to a sign, namely labored breathing Obviously, labored breathing can occur in the absence of the sensation of dyspnea By analogy, energy deficit evokes feeding reflexes which can persist in the absence of the areas of the brain required for sensation and, accordingly, for hunger Thus, Goltz[10] observed a dog from which both cerebral hemispheres had been completely removed and found that the animal regulated its food intake and maintained normal weight The anencephalic infant shows essentially normal feeding behavior

All of this is not to say that the higher brain centers and psychic activity do not participate in the regulation of food intake Clearly, they do The extent to which they do increases with ascent of the phylogenetic scale, so that,

in man, they assume much importance. The point of view that I wish to convey is that it cannot be gratuitously assumed that intensity of hunger and appetite are always quantitatively correlated with food-taking, either as determinants of the process or as reflections of it. Studies of hunger and appetite must be colligated with studies on food intake and energy balance.

Admittedly, common experience teaches that, in a general way, the intensity of hunger and appetite is correlated with the amount of food eaten. It is unlikely, however, that they are the sole determinants of food-taking behavior. Those physiological regulatory processes in which psychic events participate have an underlying "automatic" mechanism on which the mental components play.

It is usually assumed that the mechanism regulating energy balance involves only the adjustment of intake, output being an independent variable, *i.e.*, that intake is adjusted so as to equal output almost exactly. Adjustments of output do occur, however, and they contribute to the balancing mechanism. Thus, for example, when the body incurs a significant energy deficit, basal metabolic rate falls. To what extent factors of this type may operate within the physiological range of energy imbalance is not known. For the present discussion, however, we shall consider mainly the regulation of intake.

Definitions

Poinsot, the mathematician, once said: "If anyone asked me to define *time*, I should reply 'Do you know what it is that you speak of?' If he said 'Yes', I should say 'Very well, let us talk about it.' If he said 'No', I should answer, 'Very well, let us talk about something else.'" Perhaps it would be wise to heed this example to avoid logomachy. In my own excursions into the literature on the subject of hunger and appetite, however, I have sometimes been so perplexed by the babel of terms that I believe it will be helpful, to me at least, to state as tersely and explicitly as possible what it is I intend to discuss.

Hunger is the complex of sensations evoked by depletion of body nutrient stores.

Appetite has been variously defined as sensation and as desire. For the present discussion, I shall define *appetite* as the desire for food, an affective state.

For lack of a better term, I have selected *fullness* to designate the complex of sensations associated with repletion of body nutrient stores. *Satiety* is the corresponding affective state in repletion signifying a lack of desire to eat or, more precisely, a desire *not* to eat (*vide infra*). It is reasonable to assume that, between the sensations of hunger and fullness and between the affective states of appetite and satiety, there must lie a neutral zone in which the psychic correlatives of energy balance are absent. A corollary of this view is that fullness and satiety are positive psychic states and do not represent merely the absence of hunger and appetite.

Figure 1 presents a schema interrelating these factors. For the body states of depletion and repletion, the corresponding behavioral states are indicated. The behavioral states are divided into learned and unlearned, the psychic

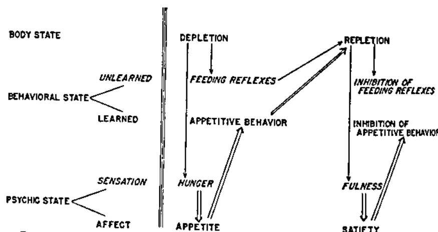


FIGURE 1 Schematic representation of relations between behavioral and psychic states in depletion and repletion Single lines represent unlearned, and double lines learned pathways

states, into sensation and affect. Before learning has occurred, as in the infant, depletion calls forth hunger sensations and unlearned feeding reflexes. The latter lead to repletion which, in turn, produces the sensation of fullness Repetition of this cycle eventually leads to learned behavior in association with affective responses Thus, the sensation of hunger evokes a desire for food, appetite, which, in turn, leads to appetitive behavior, learned food-seeking [illegible] behavior

An Approach to Integration

The eating of food is a motor act performed by voluntary muscles Like all voluntary muscles, those concerned with eating are under the control of the central nervous system. Many parts of the central nervous system participate in this control, but certain areas of the hypothalamus are especially concerned. Brobeck and his co-workers[3] have described two such hypothalamic areas, both located at the level of the ventromedial nucleus Feeding reflexes are facilitated by activity of the more lateral area and are inhibited by activity of the more medial area In FIGURE 2, a diagram is presented showing some of the theoretically possible relations of these areas and of factors acting on them. [illegible]

[illegible] the areas themselves, we may construct a flexible and comprehensive framework on which our ideas concerning regulation of nutrient balance may be arranged and examined ¶ The diagram in FIGURE 2 uses the hypothalamic areas as examples of brain regions controlling feeding The relations indicated are hypothetical The factors listed are not known to act on these brain areas

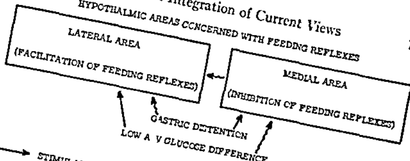


FIGURE 2 Schematic representation of possible relations between hypothalamic areas and factors which have been proposed as regulators of their activity

It is also intended to indicate that, theoretically, any one factor could produce its effect by acting on either of the hypothalamic areas, or possibly on both of them. For example, inhibition of feeding reflexes by gastric distention could be accomplished either by stimulation of the medial inhibitory area or by inhibition of the lateral facilitatory area Studies on ablation of the medial area[22] suggest that factors which normally contribute toward bringing about cessation of eating, such as gastric distention, act mainly through this medial area.

Some Factors Which May Participate in Regulation of Food Intake

Turning now to a consideration of some of the individual factors which have been proposed as playing a role in regulation of food intake, it must be emphasized (1) that it is unlikely that any one factor plays a predominant role and (2) that a change in one factor may alter the effectiveness of other factors. I have selected for consideration those mechanisms which have recently received the most attention from investigators in this field

Mayer's Hypothesis of the "Glucostatic" Regulation of Food Intake

(A) *The hypothesis*[23,30] "Glucoreceptors" in the central nervous system (probably the hypothalamus) are sensitive to the rate at which glucose is being utilized by them Low utilization rates excite neural activity leading to hunger sensations and food-taking High utilization rates produce the opposite effect. Arteriovenous glucose differences serve as an index of utilization rate and, for most purposes, peripheral (finger blood—antecubital vein blood) A-V differences serve as an index of rate of utilization by the glucoreceptors in the central nervous system

(B) *The evidence* A variety of types of evidence have a bearing on the glucostatic hypothesis Much of the pertinent evidence will be considered, but it is the opinion of this writer that studies on the relation between glucose utilization rates and food consumption are the most pertinent and crucial.

1 *Blood-glucose levels and gastric-hunger contractions.* Bulatao and Carlson[6] reported that the intravenous infusion of 5 to 10 grams of glucose in the form of 50 per cent glucose solution markedly or completely suppressed gastric contractions in fasting dogs. The inhibition was maximal within a minute or two and then subsided, the normal amplitude and frequency of contractions being restored in less than one hour. Injection of hypertonic saline or lactose was reported not to produce this effect. Although Templeton and Quigley[45] originally reported that they had confirmed this finding, in a later and more extensive study, Quigley and Hallaran[36] concluded that glucose infusion had no effect on fasting gastric motility and that the occasional transient inhibition seen in these studies was attributable to the manipulation incident to intravenous injections. Mulinos[35] came to the same conclusion from an extensive series of investigations involving 87 studies on 11 dogs. Mulinos pointed out that the occasional inhibition which occurred after injection of glucose subsided long before the blood-sugar level returned to the control level. Templeton and Quigley[45] found that the motor activity of the vagally denervated Heidenhain pouch was uninfluenced by intravenous glucose injection. Intragastric or intraduodenal instillation of glucose regularly inhibits contractions of the vagally innervated or vagally denervated stomach, but this effect is mediated by a hormonal mechanism (enterogastrone) from the upper portion of the small intestine, and is not dependent on the occurrence of hyperglycemia.[11]

In studies on human subjects, Stunkard and Wolff[44] reported that the intravenous injection of 50 cc. of 50 per cent glucose promptly abolished gastric contractions in normal subjects, but not in subjects with either uncontrolled diabetes mellitus or "hunger diabetes."

In human subjects, Scott *et al.*[37] and, in dogs, Mulinos[35] found no correlation between the occ[illegible] blood-
glucose levels [illegible]
as measured by [illegible]
glucostatic hypothesis [illegible]

The evidence is thus seen to be contradictory and inconclusive. Since, however, gastric contractions may not be a reliable index of hunger sensations and feeding beh[illegible] best not to place too mu[illegible]

[illegible] ve been [illegible] sensations [illegible] owitz and [illegible] that hunger sensations were unaltered by intravenous injection of glucose, whereas Stunkard and Wolff[44] state that the subjective experience of hunger was promptly abolished by such treatment. In a recent study in our laboratory[12] the effect of [illegible] administration of glucose on [illegible]
of saline. [illegible]
neither the test subjects nor the interviewer who recorded the data knew which treatment had been administered. The results, summarized in FIGURE 3, indicate that hyperglycemia produced by intravenous or alimentary-glucose administration produced a slight suppression of appetite (not statistically sig-

nificant), which was very much less than that produced by eating a small breakfast.

Van Itallie *et al* [44] correlated A-V glucose differences with hunger feelings in five normal and one uncontrolled diabetic subject. They interpreted their findings to support the view that, in general, a satisfactory correlation existed between A-V glucose differences and desire for food. They state that, when this difference was more than 15 mg. per cent, hunger was never reported and that persistent low differences were invariably accompanied by hunger feelings

3. *Hyperglycemia and food consumption* *A priori*, one might assume that the glucostatic hypothesis could be put to a simple and crucial test, namely, a study of the effect in normal animals and human subjects of experimentally induced hyperglycemia (with attendant elevation of "utilization rate" as measured by A-V glucose difference) on the quantity of food eaten This study would constitute an experimental "counter proof" in the sense of Bernard.[4] Here again, however, the evidence is contradictory and awaits resolution

Janowitz and Grossman[18] injected 15 cc of 10 *per cent* glucose intraperitoneally twice daily in rats and found that the slight depression of food intake that resulted from this treatment was no greater than that which occurred with control injections of saline In studies on dogs, Janowitz *et al* [22] gave large infusions of glucose intravenously (providing as much as 100 per cent of the control voluntary caloric intake) and found that the mean food consumption was unaltered when compared with no treatment or control saline infusions In these studies, food was offered to the dogs soon after completion of the infusion and was removed after 45 minutes, so that all measurements of food [illegible]

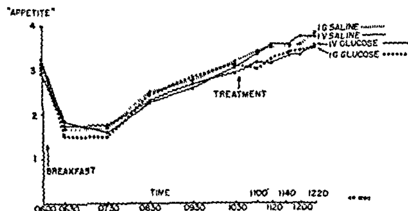


Figure 3 Twelve normal male subjects received saline and glucose intragastrically and intravenously in random order on four test days Appetite was scored by interview on a scale of five steps ranging from "no desire to eat" to "intense desire to eat" Each subject ate a fixed breakfast (450 calories) immediately after the first interview of each test

depression of food consumption. In this study also, the observations were made during the period of hyperglycemia.

Mayer and Bates[31] gave 1 cc. of 37 5 per cent glucose subcutaneously twice daily for 23 days to rats and found approximately 10 per cent decrease in food intake when compared with a control group receiving saline injections When the control and treated groups did not eat the same amount during the pre-experimental period, a correction was applied to the data compensating for this difference This experiment is the only study in the literature in which depression of food intake in normal animals has been reported to occur as a result of glucose injections

Smyth *et al*[41] gave infusions of 10 per cent glucose intravenously to two normal subjects three times daily following each meal and found no suppression of voluntary food consumption

We[12] have recently conducted a study of nine normal male test subjects in which glucose or saline was given intragastrically or intravenously just before a test meal which the subjects could consume *ad libitum*. Two saline controls and two glucose tests were performed on each subject by each route The dose of glucose was 200 cc. of 10 per cent solution intravenously and 200 cc of 25 per cent solution intragastrically. The subjects did not know what the test substances were, and they did not know that the purpose of the study was to measure food intake The control and test treatments were applied in a randomized order by a Latin square design. The results are summarized in TABLE 1 No significant depression of food consumption occurred in association with the glucose treatments, although these produced marked hyperglycemia and elevation of A-V glucose differences

4 *The effect of insulin on food intake.* Almost all investigators who have studied the problem have found that insulin increases food consumption[9, 18, 26, 31 34 40] At first glance, this would seem to support the glucostatic hypothesis During the initial phase of the action of insulin, while hypoglycemia is increasing, peripheral A-V glucose differences are elevated.[42] During the

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at this time Mayer[46] has recognized that uptake of glucose by the brain, as a whole, is insensitive to the action of insulin,[10] but he makes the "pragmatic

TABLE 1
EFFECT OF INTRAVENOUS OR INTRAGASTRIC GLUCOSE ON CONSUMPTION OF TEST MEAL BY HUMAN SUBJECTS

Route	Control		Test	
	Treatment	Calories	Treatment	Calories
Intragastric	200 ml Saline	1319	200 ml. 25% Dextrose	1260
Intravenous	200 ml Saline	1333	200 ml 10% Dextrose	1292

Each value is the mean of 18 tests on 9 subjects
For the difference between control and test, in both instances $F < 1$, $P > 0.05$, not statistically significant.

assumption" that the glucoreceptors in the central nervous system behave as the peripheral tissues do in this regard and not as brain tissue does in general. Even if this gratuitous assumption is granted, it fails to explain the action of insulin on hunger. A more reasonable explanation would appear to lie in the fact that insulin-induced hypoglycemia reduces utilization of glucose by the brain but not by the peripheral tissues.[15] The glucoreceptors concerned with hunger would then be considered to behave as does brain tissue generally. Elsewhere,[19] we have proposed the concept that hypoglycemia is an emergency mechanism in the regulation of hunger, not operating in the physiological range of blood sugar variations and, in this respect, being analogous to the role of anoxemia in the regulation of respiration.

The assumption that the glucoreceptors in the central nervous system behave as do the peripheral tissues encounters another difficulty in the explanation of the depressing effect of epinephrine on hunger. Epinephrine produces hyperglycemia with decreased peripheral, but not central A-V glucose differ-

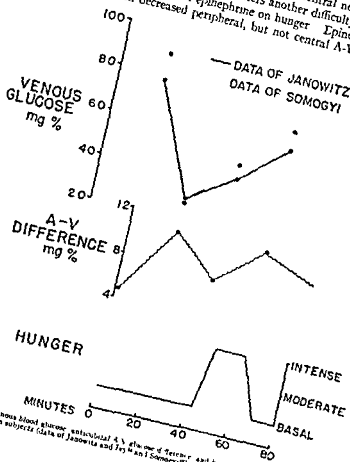


Figure 4. Venous blood glucose, antecubital A-V glucose difference, and hunger sensations after injection of insulin in human subjects (data of Janowitz and Ivy and Somogyi).

ences In this instance, Mayer[29] assumes that the glucoreceptors concerned with hunger behave as does the remainder of the central nervous system.

5. *Comment* Under controlled experimental conditions, we have found that hyperglycemia with elevated A-V glucose difference did not significantly de- [illegible]

operate under unusual conditions, but it does not appear to play a major role in normal regulation

Gastric Contractions and the Sensation of Hunger

The classical studies of Cannon[7] and Carlson[8] established unequivocally that contractions of the empty stomach produce distinctive sensations localized to the epigastrium Cannon and Carlson chose to define hunger as being this sensation Carlson[8] expressed the opinion that the other sensations associated with nutrient depletion were secondary to and dependent on the occurrence of gastric contractions, and this suggestion served as the basis for considering the gastric contractions as the central phenomenon of hunger

If hunger is defined as the complex of sensations associated with nutrient depletion, including but not limited to the epigastric pang produced by contraction of the stomach, then it can be shown that the only element of the hunger complex dependent upon stimuli arising from the stomach is the epigastric pang, and that, in its absence, the remainder of the sensation complex still occurs Therefore, the assumption that hunger sensations other than the epigastric pang are dependent on the occurrence of gastric contractions would appear to be unwarr[illegible] epigastric pang as the essential

Hunger, as a sensation, c[illegible] entire stomach in man does not abolish hunger sensations[17, 27] Unfortunately, those who have made observations on totally gastrectomized patients have not reported on whether the epigastric pang is abolished, although presumably it would be We[14] studied the effect of insulin injection on hunger sensations before and after vagotomy or splanchnicotomy in human patients Neither of these procedures abolished the hunger response to insulin, although both prevented the occurrence of the epigastric pangs in association with insulin-induced hunger From these studies, we have arrived at the conclusion that the epigastric pang associated with gastric contractions is but one element in the complex of sensations comprising hunger, and that its elimination does not significantly alter the general pattern of hunger sensation.

Gastric Distention and Regulation of Food Intake

A considerable length of time is required for the digestion and assimilation of nutrients after their ingestion If the quantity of food eaten is to be adjusted to the magnitude of the nutrient deficit, mechanisms must exist for sensing the quantity of nutrients ingested before they undergo metabolism One such possible mechanism is distention of the stomach by the ingested food,

and experiments on this subject have revealed that such distention does, i influence the quantity of food eaten.

In studies designed to evaluate the effect of gastric distention on food in it is necessary to take into account the possible role of digestion and abs tion of foodstuffs. The use of nutritionally inert materials as distenc agents obviates this complication. In studies on dogs, we[28] have used g arabic, celluflour, and water-filled balloons for this purpose. In dogs weigh 10 to 15 kg., the introduction of 50 to 100 grams of gum arabic into the stomac via gastric fistula, just before offering food, did not significantly decrease foo intake. One hundred grams of celluflour, a bulkier material, producec moderate depression of food consumption. Water-filled balloons placed in the stomach and allowed to remain there for several weeks produced sustained depression of food intake. When the amount of water in the balloon occupied a volume equivalent to 75 per cent of the volume of food eaten during the con- trol period, food intake was decreased by about 50 per cent. An inhibitory effect of gastric distention on the duration of sham-feeding in esophagosto- nized dogs has also been demonstrated.[21, 23] Since animals with denervated astrointestinal tracts show normal regulation of food intake,[17] it must be assumed that either the gastric distention mechanism is dispensable or that gastric distention may operate through somatic nerves stimulated by increase in the volume of the abdominal contents.

Within certain definable limits, animals will increase the volume of food eaten to compensate for dilution of food with calorically inert substances.[2, 20, 41] The effectiveness of gastric distention as an inhibitor of eating must, therefore, be subject to alteration when other factors regulating food intake change. Here, then, is an instance of dynamic equilibrium between factors regulating food intake.

The Effect of Energy Load on Food Intake

If the energy content of the body, in the form of stored nutrients, were the primary determinant of further food intake, it would be anticipated that, by increasing body-energy content by parenteral or intragastric feeding, voluntary oral food intake would be correspondingly decreased. When this hypothesis is put to an experimental test,[23, 30] it becomes apparent that the body does not make rapid and fine adjustments to induced positive energy loads by decreasing voluntary oral food intake. Only when extra energy intake has persisted for some time does downward adjustment of oral intake begin to occur. For example, we[28] found that, in dogs, the daily intragastric administration of one third of the *ad libitum* control food intake for four weeks did not suppress oral ntake and that intragastric administration of one half the control intake for hree weeks resulted in a decrease in oral intake to 70 per cent of the control vel. A striking finding in these studies was that body weight did not in- ease, although the combined oral and intragastric intake was considerably in excess of the control *ad libitum* level. For example, dog No. 3, in the study cited above,[28] had maintained a constant body weight of 12.2 kg. on an *ad libitum* intake of 950 calories per day. When 325 calories per day were given intragastrically for 28 days, the average daily caloric intake (intragastric plus

oral) rose to 1332 Thus total intake was 382 calories per day greater than during the control period, giving a total of 10,702 cumulative extra calories for the 28-day period Body weight remained constant, although this number of calories would be expected to produce about a 2 kg weight gain had they been stored as body tissue This finding suggests either that a change in body composition may be induced by extra calorie intake or that mechanisms may exist for expending calories in excess of requirements for maintenance.

Stimulation of Head Receptors in Regulation of Food Intake

If a dog is allowed to eat a portion of its food a short time before food is offered *ad libitum*, the voluntary intake is reduced by an amount approximately equal to the prefeeding.[22] If, instead of allowing the dog to eat the portion of food, the food is placed in the stomach just before food is offered *ad libitum*, voluntary intake is suppressed to a lesser extent. If the portion of food be placed in the stomach a number of hours before food is offered, no suppression of oral intake occurs. Conversely, in dogs with esophagostomy,[21, 23] sham-feeding, in which the food fails to reach the stomach, results in the taking of far greater quantities of food than in intact animals. From these observations, we may hypothesize that stimulation of head receptors by smelling, tasting, chewing, and swallowing, during eating, plays an important role in bringing about satiety and suppression of further eating, but that this factor is relatively ineffective when it is not associated with entry of food into the stomach. Even when an amount of food greater than the quantity which the animal voluntarily eats during a control period is given daily intragastrically, oral intake of significant quantities persists for at least several weeks

In rats, a comparison has been made of the effect of food introduced by gastric fistula and food eaten normally by mouth. As measured by rate of [illegible]

Thus, stimulation of head receptors is an important element in the group of factors which normally contribute to satiety.

Interrelation of Factors Regulating Food Intake

Factors stimulating intake of food. Although energy balance results from [illegible]

[illegible]

Factors limiting intake of food. What causes cessation of eating? The simplest answer to this question is that eating leads to cessation of eating. The ingestion and assimilation of food can be divided, for purpose of analysis, into

the following components: (1) *oropharyngeal*, introduction of food into the mouth, chewing and swallowing, (2) *gastrointestinal*, entry of food into the stomach and intestines with subsequent digestion and adsorption, (3) circulation of absorbed nutrients in *blood*, and (4) extraction of nutrients from blood by *tissues* for storage or oxidation The oropharyngeal component is potent when acting with the gastrointestinal component, weak when acting alone The gastrointestinal component appears to involve mainly distention Inert bulk in the stomach is as effective as an equal volume of food in suppressing eating Of the four components listed, this factor is the only one which has high effectiveness when acting alone The importance of the blood component has not been clearly established Of the major nutrients, carbohydrate, as represented by blood glucose, has received the most attention Hyperglycemia, with rapid uptake of glucose by tissues, does not, when acting alone, produce marked inhibition of eating The role of the tissue factor can only be presumed Prolonged overloading of the body with extra calories eventually leads to downward adjustment of voluntary food intake It has not been demonstrated that this adjustment is associated with extra storage of food energy in tissues The mechanism of the effect is obscure

Concluding Remarks

The aim of this presentation has been heuristic This is not a comprehensive archive of recent work It is intended more to pose questions for future investigation than to cull answers from past inquiries These major points were considered Hunger and appetite are psychic correlatives of the bodily processes which regulate nutrient balance They arise from, and participate in, the regulatory processes Food-taking is a motor act of skeletal muscles, governed by nervous processes like all other voluntary muscles Specialized hypothalamic areas participating in this control have been discovered Among the factors which may regulate the activity of these hypothalamic centers and of other brain areas concerned with feeding are oropharyngeal stimulation, gastrointestinal distention, blood levels of nutrients (particularly glucose), and tissue stores of nutrients For none of these factors is the mechanism of action known

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Discussion of the Paper

Doctor Leon Moses (*College of Physicians and Surgeons, Columbia University, New York, N Y*) I was most pleased to hear Doctor Grossman stress that, in the total understanding of the dynamics of normal weight and obesity, both the factors of food intake and energy output will have to be considered

In the intensive psychoanalytic study of obese individuals, one is definitely impressed that there is a psychodynamics of the excessive muscular inactivity as well as the excessive food intake In many adolescent and young adult patients with moderate obesity of 20 to 40 pounds, this factor of physical inactivity is very conspicuous It is definitely present, though less prominent, in all adult obesity cases The obesity is most probably related to both the increased food intake and diminished energy output

Aside from the complex psychodynamic factors of excessive food consumption which also influence the tendency to excessive muscular inactivity, there are specific unconscious fantasies of ego inadequacy and incompetence that account for the physical passivity These fantasies lead to excessive inhibition of all executive motor functions, especially in the social, sexual, and muscular areas The end result of such inhibition is diminished muscular activity with resultant limitation of energy output

In the clinical medical and psychotherapeutic management of the obese, these total psychodynamic factors will have to be considered

Doctor Theodore B Van Itallie (*St Luke's Hospital, New York, N Y*). The subject of glucose arteriovenous differences has come up a number of times during the previous papers It is important to emphasize that glucose A-V differences are not the foundation of the glucostatic theory, and could not be, since there are inherent limitations to the use of peripheral glucose A-V differences as indices of carbohydrate utilization elsewhere in the body Such A-V differences have been studied by us merely in an attempt to obtain more reliable information about the changes which take place in carbohydrate supply than is available from arterial or venous glucose determinations alone Moreover, it should be stressed that we originally studied glucose A-V differences in non-obese subjects who were consuming diets of varying composition and caloric

content, and who were adjusted to the diets. In such studies, food was administered in physiologic fashion *via* the gastrointestinal tract.

Recently, Doctor Morgan, Doctor Dotti, and I have become interested in determining the conditions under which A-V differences could be regarded as valid indices of *peripheral* uptake of metabolites. We suspected that diffusion phenomena *per se* might modify A-V differences and hence give a distorted [illegible]

are not utilized peripherally in man, any A-V differences observed must be due to diffusion "delay" When these substances were administered intravenously, relatively large positive A-V differences were measured on the rising slope and at the peak of the curve. These differences obviously were not due to uptake of the substances by peripheral cells and, indeed, the A-V differences became inverted on the falling limb of the curve Thus, peripheral glucose A-V differences measured during a moderately rapid rise or fall of blood-glucose level must be interpreted with caution. This is particularly the case when glucose is given intravenously.

I should like to comment on the acute experiments in which Doctor Grossman gave glucose intravenously to dogs and to human subjects He states that he observed only slight changes in the spontaneous food intake shortly thereafter I should have been surprised if marked changes had been noted As Doctor Brobeck already has pointed out, Doctor Grossman's findings underline the well-recognized importance of habit and conditioning factors in determining human and canine behavior. They do not throw much light on the glucostatic hypothesis Also, as Doctor Janowitz has pointed out so ably, we must consider adaptations to changes in intake from a greater time perspective if we are to interpret the results properly. I wonder whether Doctor Grossman might not get quite different results if he repeated his experiments on a longer term basis.

Certainly, all of us here have had the experience that a rather large sampling of hors d'oeuvres at a cocktail party, to say nothing of the cocktails, does not necessarily inhibit and may, indeed, increase consumption of the roast beef and potatoes which follow.

Incidentally, Albright and his group gave glucose intravenously to patients over a prolonged period of time as the main source of calories and found that such patients did not experience hunger even though their stomachs remained empty and the caloric intake was somewhat below requirement levels[2] We have observed similar effects of intravenous glucose in our parenteral feeding experiments

As far as insulin effect on A-V glucose differences is concerned, this is rather a complicated matter. Insulin increases glucose uptake in various portions of the body and thereby lowers arterial glucose levels. In response to the blood glucose fall, if it is appreciable, insulin-antagonistic substances apparently are

[1] 1954 Federation Proc 13 156

[2] 1944. Transactions of the 8th Conference on Metabolic Aspects of Convalescence. 7 168-172 Josiah Macy, Jr Foundation New York, N Y.

creted in increasing amounts, as Somogyi has shown. It has been demon-

glucose available to certain areas purely by lowering arterial glucose below a threshold value. This primary effect is then reinforced by insulin antagonists such as epinephrine and, perhaps, growth hormone, secreted in response to the insulin-induced hypoglycemia. Such inhibitory effects on peripheral utilization persist even after the blood glucose starts to rise that is one of the reasons the blood glucose level does rise

Thus, insulin may make glucose temporarily more available to certain insulin-sensitive areas and, at the same time, may act so as to exclude glucose from other parts of the body less sensitive to insulin action Until more is known about the specific effect of insulin on the various tissues of the body, the effects of insulin on hunger necessarily will be difficult to interpret

[1]1952, J Clin. Invest. 31 717

content, and who were adjusted to the diets. In such studies, food was administered in physiologic fashion *via* the gastrointestinal tract.

Recently, Doctor Morgan, Doctor Dotti, and I have become interested in determining the conditions under which A-V differences could be regarded as valid indices of *peripheral* uptake of metabolites. We suspected that diffusion phenomena *per se* might modify A-V differences and hence give a distorted picture of the degree of uptake of a metabolite actually taking place at a given time. To test this possibility, we measured peripheral A-V differences of intravenously injected sucrose and sorbitol in man[1]. Since these substances are not utilized peripherally in man, any A-V differences observed must be due to diffusion "delay." When these substances were administered intravenously, relatively large positive A-V differences were measured on the rising slope and at the peak of the curve. These differences obviously were not due to uptake of the substances by peripheral cells and, indeed, the A-V differences became inverted on the falling limb of the curve. Thus, peripheral glucose A-V differences measured during a moderately rapid rise or fall of blood-glucose level must be interpreted with caution. This is particularly the case when glucose is given intravenously.

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[1] 1954. Federation Proc. 13: 156.
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secreted in increasing amounts, as Somogyi has shown It has been demonstrated by Bell and Burns[8] that insulin given intravenously decreases femoral A-V glucose differences merely by lowering the arterial glucose level. Given intra-arterially, insulin widens A-V glucose differences in the injected extremity. Hence, insulin injection might increase hunger by making less glucose available to certain areas purely by lowering arterial glucose below a threshold value This primary effect is then reinforced by insulin antagonists such as epinephrine and, perhaps, growth hormone, secreted in response to the insulin-induced hypoglycemia. Such inhibitory effects on peripheral utilization persist even after the blood glucose starts to rise· that is one of the reasons the blood glucose level does rise

Thus, insulin may make glucose temporarily more available to certain insulin-sensitive areas and, at the same time, may act so as to exclude glucose from other parts of the body less sensitive to insulin action Until more is known about the specific effect of insulin on the various tissues of the body, the effects of insulin on hunger necessarily will be difficult to interpret

[8] 1952 J Clin. Invest. 31: 717

Part III. Clinical Aspects

FOOD PREFERENCES IN MAN: SPECIAL CRAVINGS AND AVERSIONS

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1 *Food Cravings and Aversions in Disease*

Urgent cravings for, as well as aversions toward, foods or special nutrients are known to occur in a number of medical conditions In these circumstances, the appetite is often perverted, and a craving for abnormal, sometimes loathsome, substances develops Such perverted appetite is usually designated as pica, a condition especially frequent in pregnant women and in children. The cravings and aversions of pregnant women are generally known, even among laymen No explanation has ever been given for this remarkable phenomenon unless one is willing to accept the Freudian conceptions of recent years Nevertheless, the possibility exists that, one day, a reasonable basis for the pica of pregnant women may be found

In this connection, the habit of certain tribes to eat clay of riverbanks should be mentioned This so-called geophagia is considered to have a salutary influence because, by this custom, certain deficiencies in nutrition can be repaired A comparable explanation may exist for the tendency of small children to eat earth, dirt, chalk, or ashes—a habit that usually disappears when the children reach the age of three or four years. The underlying cause may be a craving for certain minerals and vitamins in which their diets are deficient. The pres- [illegible]

of these children are suffering from an intestinal disease. The earth and ashes could then act as absorbents, like kaolin, charcoal, or bismuth, and thereby have a favorable effect Still other physicians see a connection between this craving and intestinal parasites.

When children scratch chalk from walls and eat it, they may well be urged by a calcium deficiency This tendency occasionally may lead to a dangerous complication Where the walls are covered with lead-containing paint, lead poisoning frequently results from this habit Some children have an urge to suck on hairy objects The swallowed material then may accumulate in the stomach, resulting in the formation of large hair balls and bezoars, which ultimately require surgical intervention.

In many cases, the neurotic disposition of the child seems to be the cause of this pica Especially when this remarkable abnormality persists after the child has received adequate medical care and nutritional guidance, the presence of grave psychiatric abnormalities must be considered Schizophrenic children may even indulge in coprophagia.

Comparable cravings are well known in animals In South Africa, where the

soil is poor in phosphates, the cows develop osteophagia. At night, crossing the plains of this large country, the traveller may hear the crunching of bones devoured by the phosphate-hungry cattle. Chickens denied calcium-sufficient diet and faced with a difficult quest for it (in places such as the Amazon River Basin) replenish their systems by the habit of eating the shells from eggs they have themselves produced.

Before Minot discovered the curative influence of liver administration in pernicious anemia, this disease was always fatal. It was characterized by successive relapses and favorable remissions, succeeding one another without apparent reason. Ultimately one of these relapses always terminated fatally, and clinicians of wide experience, in the last decades of the 19th century and the first decades of the 20th, agreed that they never had seen permanent recovery in a patient with pernicious anemia. Nevertheless, after the liver treatment had been introduced, a few patients with pernicious anemia were discovered who, thanks to their own uncommon appetite for beef liver, had managed to stay alive.

It is known that tribal wars have been fought for the possession of certain areas rich in salt. Whether these sacrifices in human life were made only to obtain large amounts of NaCl for seasoning, or whether NaCl rich in iodine was desired in order to prevent the development of endemic goiter is a question deserving consideration.

For a long time, it has been known that patients with insufficiency of the adrenal cortex occasionally crave salt. Better understanding of the fundamental changes of electrolyte metabolism in Addison's disease has elucidated the important therapeutic implications of this craving. In the absence of certain hormones elaborated by the adrenal cortex, excessive loss of sodium in the urine sets in, leading to the characteristic hyponatremia of the Addison patient. This abnormality of electrolyte metabolism is responsible for the causation of part of the dangers which threaten the lives of these patients. Since hyponatremia can be neutralized, at least partially, by the lavish administration of salt, this craving may have prolonged life in some of these patients.

The craving for food—especially for sweets—of obese patients has remained unexplained for a long time. Chronic, moderate hypoglycemia, which often has been considered a possible cause for craving for sweets, has been found very rarely in obese heavy eaters. Recently, thought and discussion have been given to the possibility that a localized cerebral hypoglycemia, an abnormally low blood sugar of the venous blood, returning from the brain, may play a role in the causation of this craving for sweets.

Patients with functional postprandial hypoglycemia often crave sweets. Contrariwise, it is noteworthy that patients with hypoglycemia due to an island cell tumor of the pancreas very seldom are aware, by instinct, that the eating of sweets could at least temporarily alleviate their attacks of sweating, tremor, incoherence, or unconsciousness.

There are, of course, many diseases which are complicated by anorexia, nausea, and a loathing of food. It would be quite an undertaking to list all these different afflictions. Special mention may be made, however, of the lack of ap-

petite in hepatitis, because this symptom often precedes the first objective signs of the disease.

Loathing of meat, a complaint of so many patients with carcinoma of the stomach, must have been known for centuries. This *horror carnis* has never been explained beyond reasonable doubt. Occasionally, it occurs in patients [illegible]

occur, they are rarities In the majority of patients in whom loathing of food causes fatal cachexia, psychological disturbances prevail. Thus, correctly, most of the cases exhibiting this syndrome are nowadays designated as anorexia nervosa

Loss of appetite, sometimes even aversion of food, as a side action of many different medicaments, is of course frequently encountered. In the case of the benzedrine compounds, this undesirable side effect has been successfully directed into therapeutic channels.

Thus, certain cravings and aversions, as presented by patients with different diseases, can be explained, at least partly. Many such nutritional preferences or aversions seem to lack a somatic basis, and have to be ascribed to psychologic disturbances

2. *Nutritional Food Cravings*

Better known, and of even greater importance, are preferences for certain nutrients, aversions to others, as found among different peoples of large ethnic groups Part of these nutritional cravings and aversions can be explained by economic conditions, agricultural necessities, and religious laws Food habits, however, are also dependent upon customs which people have been educated to accept during the years of their childhood, in their parental homes The child is taught not only what to like, but he is also told what to abhor. Americans crave milk, ice cream, and coffee; Germans, beer; Frenchman, wine; Britishers (at least before the last World War), beef and port; Bostonians, beans; the Dutch, "hutspot", all because dietary routines and habits which these peoples were obliged to follow, or learned to admire as children, molded their preferences and distastes No other rationale exists for these preferences. The American child sees that his father [illegible]. Therefore, when he [illegible] e same way, [illegible] nk wine or beer The European child observes that, in his family, no adult drinks milk. After his 12th birthday, he resents being treated as a child. He then wishes to act as adults do and, therefore, he steadfastly refuses to drink milk. In Europe, a fat boy is considered ridiculous He becomes automatically isolated because his overweight makes it impossible for him to play soccer. The attitude of children to the problem of obesity is evidently different in the United States. The difference can be judged from the way American children crave excessive quantities of ice cream and candy, bringing upon themselves the unavoidable consequence of obesity.

lar nutrient are rationalized by stressing its favorable influence upon the health of the population

ucts This is an unavoidable necessity, in view of the overpopulation of many of the Oriental countries and the depletion of the soil due to primitive methods of agriculture and erosion. As a result of the overpopulation, the areas which can be allotted to cattle raising are of necessity extremely limited. In order to produce a given number of calories, both cattle breeding and fish culture—that is, the production of animal food—need surface areas much larger than those required for the production of the same number of calories in the form of vegetable fat and protein To assure a sufficient caloric intake, the soil of the overpopulated areas, therefore, must be reserved almost exclusively for vegetable crops, and meat necessarily becomes a scarce and expensive nutrient.

In most of the standard diets of the Western world, the relation by weight of carbohydrates to protein and fats varies around 4:1:1; that is, about 55 per cent of the total caloric intake is derived from carbohydrates, 14 per cent from proteins, and 30 per cent from fats In the Orient, however, 80 to 85 per cent, sometimes even 90 per cent of all the calories are derived from carbohydrates, 5 to 10 per cent from protein, and about 7 to 8 per cent from fats Even this small amount of proteins is mainly of vegetable origin. The amount of calcium and of certain vitamins is usually small. Since no animal food is used, the

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lack of vitamin D intake is not felt in the tropical part of the Orient, where, under the influence of ample sunshine, sufficient vitamin D is formed in the skin Avitaminosis D, however, is frequent in the northern provinces of China, where lack of sunshine is combined with lack of vitamin D intake.

The diet of the Oriental differs from our daily diet not only because it is so low in protein, fats, and certain vitamins, but also because the daily caloric intake in the Orient is small as compared with the West Diet surveys made both in Java and India have indicated that the caloric intake of large parts of the population of Java, India, and Ceylon has been below the minimum requirements The average Filipino, too, receives only 2180 calories instead of the

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contrary to any preference or craving.

On the other hand, far the greater number of the Chinese loathe dairy products just as much as the Americans crave them. In this case, they respond to the influence of their customs and education Even the young Chinese who has had the privilege of a Western education can only with difficulty be persuaded to drink milk. Nevertheless, he fully realizes that food rich in fats and cholesterol, such as milk, if added to the Chinese diet, would help to build up a resistance against the ubiquitous exposure to tuberculosis in China

Milk must be mixed with cocoa to [illegible]

[illegible]

we call cheese

Many food customs which, over the course of years, have developed into cravings or aversions are in part favorable, in part injurious to health As an example, it may be mentioned that our habit of overfeeding damages the health of the population in many different ways Nevertheless, it must be an excellent protection against tuberculous infections, and it may have been an important factor in the decrease of this disease in the United States It may also be [illegible]

(1) *Beer* In Southern Germany, the excessive intake of beer leads to the so-called "Munchener beer heart" The name indicates that this disease is especially frequent in Bavaria, although it is also commonly found in other areas, where beer is the popular beverage The tremendous amount of calories consumed by excessive beer drinkers leads to obesity The chronic increase in the circulating blood volume caused by large quantities of beer is a heavy burden for the left ventricle The combination of these two factors must be pernicious for every individual who has the slightest tendency toward hypertension This fact probably explains why the syndrome of the "Münchener beer heart" con- [illegible]

[illegible]

guin ducks—whose name is derived from their erect, penguinlike posture Large herds of penguin ducks, shepherded by small boys, roam all over the island of Java, feeding in the rice fields after the rice has been harvested At night, they are driven into flimsy enclosures made of bamboo and covered by large nets In the morning, the eggs which the ducks have laid are collected, after which the flock is released to continue its peregrination to other rice fields Often the eggs are stored for a considerable time in salt and wood ash, or in salt water, in large jars Ducks are prone to suffer from different salmonella infections Since, in these birds, oophoritis is a common complication of salmonel- [illegible]

tard and thus, even in the United States, outbreaks of salmonella infection have been traced to ducks' eggs.

(3) *Craving for white rice.* Special mention must be made of the beriberi of the rice eaters of the Orient, a problem that is due at least partly, to a craving for white rice Wholly polished rice is nutritionally far inferior to "dirty" rice, that is, only partly polished rice. Rice contains 7.5 per cent of a valuable protein which, if mixed with soybean proteins, has a high biologic value Ample amounts of vitamin B, minerals, and even fat (1 to 2 per cent) are present in the *outer* layer of the rice. The loss of vitamin B_1 from rice through the milling and polishing process explains the frequency of beriberi in many rice-eating countries, especially in such areas as southern China and the Philippines, where not only the urban but also the peasant population eats, mainly, white polished rice In large rural areas of India and Indonesia, where the population eats only hand-pounded rice, beriberi does not occur. When the native women pound the rice in their primitive utensils, only the hard, outer husk is removed The outer layer of the rice proper, the silverfleece, however, remains intact, and the hand-pounded rice, the brownish looking "gabah," contains enough vitamin B_1 to protect the population against beriberi

The importance of the protective influence of the hand-pounded gabah against beriberi was recognized before the vitamin theories of beriberi had been developed A few years before the classic experiments of Eijkman proved the importance of vitamin B, this theory was eloquently propounded by van Dieren, a practicing physician in Amsterdam, who had never been in the Orient and had never had any personal experience with beriberi Van Dieren concluded, after a critical, historical survey of the literature, that beriberi developed when people were fed on white polished rice Although wrong in his contention that milled rice contained a toxic substance, he was correct in the conclusion that beriberi did not occur as long as the natives ate hand-pounded rice, and that patients having the disease improved rapidly when fed with gabah. Unfortunately, van Dieren was no experimenter, and had to defend his theory by interpreting the investigations of others. His correct conclusions as to therapy were severely criticized by the infectionists In the ensuing battle of opinion, van Dieren not only attacked the latter but, for many years, continued to defend his toxin theory also against the new discovery that beriberi was a deficiency disease Consequently, it is often forgotten that van Dieren's therapeutic solution of the beriberi problem was sound, although his theory as to [illegible]

[illegible]

man who has to eat brown, so-called "dirty" rice loses considerable face. Poor farmers have no choice but to eat their own, brown, hand-pounded rice, and remain healthy People who are in a higher income class can buy white polished rice and develop avitaminosis! The same thing was seen in Indonesia at [illegible]

mum. Only the Chinese overseers of these estates occasionally suffered from [illegible]

[illegible] at their disposal. The beriberi of the overseers demonstrated again how craving for special nutrients—in this case, white rice—may lead to disease.

The reason why millions of Orientals *must* eat the dangerous polished rice is connected with the fact that the highest concentrations of vitamins and fats of *the rice are present in the superficial layer of the kernel, just below the silverfleece* As these substances are excellent food for bacteria and insects, silverfleece rice easily, often within three weeks, becomes rancid and infested with mites and other pests. Silverfleece and half-polished rice therefore, can be eaten only by a rural population which harvests its own rice and eats it within a short time after harvesting. Many of the rice-eating areas are not self-supporting, as far as rice is concerned, and must import their rice from the three largest rice-exporting countries. Indochina, Thailand, and Burma As all the rice exported from these countries must necessarily be milled, it is impossible to feed the whole rice-eating population of the world only with partially milled, silverfleece rice. Thus, even in countries where the dangers of polished rice are fully realized, its use cannot be avoided

For centuries, the Orientals have recognized the need for additions to the rice diet. In Indonesia, mung beans are eaten in large amounts For 300 years, these beans have been known for their prophylactic influence against beriberi Highly important is supplementation of the rice diet with soybeans, an important factor in the Oriental regimen because soybeans contain large amounts of calcium, vitamin B, and valuable protein In northern China, much larger quantities are consumed daily than in southern China but, even in the south, the people eat soybean products, whenever they can get them, especially in the form of soybean sprouts. One disadvantage of the soybean is its bitter taste In northern China, this detriment is overcome by mixing soybean flour with other flours whereas, in Indonesia, soybeans are fermented with molds before they are eaten. Even if the fermentation product, which is called "tempe kedele" does not look appetizing to Western eyes, it has a pleasant taste In addition, it contains 20 per cent of protein *To prepare this dish, soybean* [illegible]

[illegible] continue this processing of soybeans and peanuts One of the advantages of these tempes consists of their easy digestibility The protein content of these tempes is more rapidly and more completely absorbed than the proteins of the original soybeans The question may be raised whether, during the fermentation by molds, penicillinlike substances are formed which are of importance in

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It is well-nigh impossible to induce all Oriental rice-eating peoples to eat the hand-pounded rice that gives such good protection against beriberi In China, for instance, there is a pronounced preference for white polished rice, and the man who has to eat brown, so-called "dirty" rice loses considerable face Poor farmers have no choice but to eat their own, brown, hand-pounded rice, and remain healthy People who are in a higher income class can buy white pol- [illegible] Indonesia at [illegible]

and the incidence of beriberi among this group went down to a negligible mini-

mum Only the Chinese overseers of these estates occasionally suffered from beriberi. These overseers, it goes without saying, earned larger salaries than the laborers and could afford to buy their own white polished rice in the village instead of accepting the despised, "dirty" silverfleece rice which the estates put at their disposal The beriberi of the overseers demonstrated again how craving for special nutrients—in this case, white rice—may lead to disease.

The reason why millions of Orientals *must* eat the dangerous polished rice is connected with the fact that the highest concentrations of vitamins and fats of the rice are present in the superficial layer of the kernel, just below the silverfleece As these substances are excellent food for bacteria and insects, silverfleece rice easily, often within three weeks, becomes rancid and infested with mites and other pests. Silverfleece and half-polished rice therefore, can be eaten only by a rural population which harvests its own rice and eats it within a short time after harvesting Many of the rice-eating areas are not self-supporting, as far as rice is concerned, and must import their rice from the three largest rice-exporting countries: Indochina, Thailand, and Burma As all the rice exported from these countries must necessarily be milled, it is impossible to feed the whole rice-eating population of the world only with partially milled, silverfleece rice Thus, even in countries where the dangers of polished rice are fully realized, its use cannot be avoided

For centuries, the Orientals have recognized the need for additions to the rice diet. In Indonesia, mung beans are eaten in large amounts For 300 years, these beans have been known for their prophylactic influence against beriberi Highly important is supplementation of the rice diet with soybeans, an important factor in the Oriental regimen because soybeans contain large amounts of calcium, vitamin B, and valuable protein In northern China, much larger c [illegible] t [illegible] f [illegible] l [illegible] other flours whereas, in Indonesia, soybeans are fermented with molds before they are eaten Even if the fermentation product, which is called "tempe kedele" does not look appetizing to Western eyes, it has a pleasant taste In addition, it contains 20 per cent of protein To prepare this dish, soybean [illegible] fermentation process of peanuts leads to the formation of so-called "ontjom," containing 20 per cent protein and 3 to 9 per cent fat Comparable fermentation products are also used in Indochina and in Surinam (Dutch Guiana, in the northern part of South America). The Javanese who emigrated to Dutch Guiana in large numbers brought their tempes with them and, even now, they still continue this processing of soybeans and peanuts One of the advantages of these tempes consists of their easy digestibility The protein content of these tempes is more rapidly and more completely absorbed than the proteins of the original soybeans The question may be raised whether, during the fermentation by molds, penicillinlike substances are formed which are of importance in

view of the frequency of streptococcus infections in the Orient. Be this as it may, the craving for tempes has a favorable influence upon the health of the Indonesian

group of ailments Such attention will clearly elucidate the fact that our craving for high-caloric, high-protein diets has, decidedly, many disadvantages For many decades, French clinicians have taught the existence of a group of diseases which they designated as the "arthritic diathesis " This group of diseases comprises arthritis urica (gout), diabetes, obesity, gall stones, and premature arteriosclerosis The latter would nowadays probably be designated as premature coronary insufficiency or coronary thrombosis. In the family of a patient who developed one disease belonging to the arthritic diathesis, as, for instance, gout, usually one or several of the other members of this group of diseases did occur In general, it can be said that, with few exceptions, patients suffering from one of the diseases of the arthritic diathesis are overfed individuals Even if a certain "diathesis" must exist for any of these diseases to develop, the disease usually becomes manifest only if too large quantities of rich food are consumed. In other words, in order for gout to develop, a clear-cut hereditary factor will usually be present Fortunately, on a diet low in purins, the tendency to gout only rarely gives rise to the development of acute gout On the other hand, a craving for a diet containing considerable quantities of roast beef, steaks, and port, as was customary in Great Britain, will favor the development of gout The prevalence of acute and chronic gout in the British Isles can be appreciated only by physicians who "walked" the wards of the hospitals of Great Britain in prewar days Senior students of the medical schools of the continent in Europe often went for a few months to England to become acquainted with the teaching of medicine in that country. These students usually served as "dressers" in the surgical wards, an assignment comparable to that of surgical clerks in the United States The continental greenhorn dresser was always confronted with one or more patients whose presenting sign consisted of a markedly painful, swollen, and apparently phlegmonous hand The tentative diagnosis of a phlegmon, which the freshman dresser usually made,

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of gout had to be considered The success of colchicine treatment easily proved the gouty nature of the pseudophlegmon.

It is of great importance to realize that, since World War II, that is, since the austerity program had to be enforced, gout has become much less common in Great Britain Among the population of Great Britain, there are nowadays just as many individuals with an arthritic diathesis as there were before the war. The austerity ... forced to live on a low ... uld not be satisfie ... has

[illegible] It follows that [illegible]

The other diseases that belong to the arthritic diathesis are also greatly dependent upon food preferences. Diabetes is a widespread disease in China but, among the poor coolies of northern China, the disease is remarkably mild, and insulin treatment is only rarely necessary. Ketosis is relatively rare, and diabetic coma is extremely rare in the poorer part of the population—fortunately so, for the price of insulin would be prohibitive for the great majority of the diabetics of north China [illegible]
diabetics in our part [illegible]
Chinese diabetics [illegible]
ble to the diets which were so warmly recommended in the preinsulin era by Von Norden in Germany, and by Allen in the United States. It is important to note that, in Batavia, in Java, where a large number of Chinese were living, most of whom had assembled considerable wealth, diabetes was a dangerous ailment. This experience presents a warm recommendation for a low caloric diabetic diet in which carbohydrate and vegetable protein prevail, with marked restriction of animal protein and fat. Such a diet might also be salutary for western diabetics.

Needless to say, the Chinese coolie diet, low in calories, low in proteins, high in carbohydrate, is also an excellent preventive agent against obesity, another member of the arthritic diathesis. The Chinese race certainly has a tendency toward obesity, as is clearly demonstrated by the overweight from which most important mandarins suffered. The coolie class, however, is well protected against this evil.

Since cholesterol occurs only in animal food, the diet of the Oriental is necessarily devoid of this lipoid. This deficiency must explain why the blood cholesterol of the Orientals is lower than the levels which are customarily found in the Occident. In the United States, blood cholesterol values of 250 to 300 milligrams per 100 cc are customary but, in the Orient, the values usually range around 150 milligrams per 100 cc. Poor coolies in northern China often have values of approximately 100 mg per 100 cc, sometimes even less.

Pathologists are still speculating about the possibility that the low blood cholesterol of the Orientals might be a genetic characteristic, like the low weight of adrenals and gonads and the scanty hair growth. Forty years ago, however, Dutch clinicians had already shown that the low-blood cholesterol of the Indonesian is not a racial characteristic. Careful investigation revealed that the blood cholesterol of Javanese serving as well-fed waiters on the luxury ships plying between the Netherlands and the Indies reached levels comparable to the average figures found in the Occident.

It is obvious that diseases connected with cholesterol infiltration can be expected to be uncommon among Orientals. This may well be one of the reasons why arteriosclerosis is a rare disease in the Orient. Although the Electrocardiography Division of the Department of Medicine of Peiping Union Medical College was a very active one, electrocardiograms showing the typical features of

coronary thrombosis were rare exceptions in the collection. There were many years when not a single case of coronary thrombosis was encountered. Other afflictions connected with arteriosclerosis were extremely rare, and amputations for diabetic gangrene were practically unknown.

The gallstone problem which is so closely related with cholesterol metabolism differs in the Orient from the Occidental gallstone disease. In the West, cholesterol stones occur in about 40 per cent of women above 40 years of age. In addition, cholelithiasis occurs four to five times more frequently in women than in men The much lower averages of the blood cholesterol values in the Orient explain why cholesterol stones do not occur in the Indies and in China. The relatively few cases of gallstones in China are by no means especially frequent in women Typhoid and salmonellosis are the prevailing infections leading to gallstone formation Since typhoid and paratyphoid occur more frequently in the male than in the female, there is a larger number of male patients with cholelithiasis in China than of female patients

Another point of some importance is the composition of the stones. As inflammatory gallstones always contain considerable quantities of calcium, the gallstones in China are nearly always radiopaque. In contrast to the experience of the Western physicians, Chinese clinicians are loath to diagnose gallstones which cannot be visualized on an X-ray film.

The hypercholesterolemia of nephrosis, however, does not depend on the cholesterol intake When nephrosis develops in poor Orientals, whose cholesterol intake is practically zero, the serum cholesterol values rise to the same levels seen in nephrosis patients in the Occident.

(5) *Sundry food preferences.* The endemic occurrence of the broad tapeworm or *Dibothriophyllium latum* in Finland is connected with the eating of insufficiently cooked fresh-water fish This disease has now become frequent in the areas of the midwestern lakes of this country, where a large number of Finns have settled The intermediate host between humans and fish in the United States is a different microscopic aquatic animal from the one in Finland The same broad tapeworm is occasionally encountered in Brooklyn, where a large part of the population eats a peculiar fish product designated as "gefullte fish" Apparently, in the preparation of this food, the mixture of raw fish and condiments is tasted by the housewife prior to cooking

The frequency of the intest[illegible] in Canton is connected with the cus[illegible]
only been dipped in hot gru[illegible]
spread also to other areas in south China. Until then, it was practically limited to Canton, due to special local conditions

The regrettable frequency of trichinosis in the United States must be the result of the custom of eating our hamburgers and other pork products insufficiently cooked This custom is a dangerous one in the United States, where the law does not require obligatory trichinoscopy of masseter muscle and diaphragm of every slaughtered hog The Chinese love pork and, since the rats of China are heavily infested with *Trichinella* carriers, the human exposure to trichinosis is apparently heavy. Nevertheless, trichinosis is a rare disease, for the Chinese eat only very well cooked meat Even if the pork which is used

for the preparation of sweet and sour spare ribs contains *Trichinella* capsules, the latter will all be killed during the preparation of the spare ribs.

Infestation of the lungs with *Paragonimus westermani* is a disease which is very frequent in Korea and Japan, where the eating of raw crabs is popular. In China, there is an aversion against raw food in general, raw crabs in particular, and there this disease is practically unknown. Only in one isolated area of the Chinese province of Chekiang does this disease occur. Here, the "drunken crab" is a delicacy. Such crabs are prepared by dunking the living crab in alcohol, allowing it to soak overnight, and eating it the following day.

Our custom of drinking irradiated milk increases the absorption of the large amounts of calcium in the American diet. In many respects this may be favorable but, under certain circumstances, it becomes a disadvantage. This food habit, in combination with the administration of extra vitamin D and calcium given by well intentioned surgeons, has contributed to the increased tendency toward formation of renal calculi after fractures. Under influence of the increased calcium absorption by vitamin D with ensuing urinary calcium excretion in an individual immobilized in a plaster cast, the frequency of renal stone disease in patients with fractures of the femur has ascended, in some of our army hospitals, to 7 per cent.

On the other hand, the low vitamin D content of the Chinese diet has not only disadvantages. In northern China, where the diet is not only low in vitamin D, but the daily amount of sunshine is either moderate or, as in Shensi and Shanshi, actually low, osteomalacia is a frequent malady. Besides, the whole population has subclinical avitaminosis D. In avitaminosis D, the calcium excretion in the urine dwindles to traces, even before hypocalcemia sets in. When no calcium is available in the urine, no calcium phosphate or calcium oxalate stones can be formed. This must be why renal stone disease is rare in most provinces of northern China having restricted exposure to the sun.

Another point of importance is the rarity of amyloidosis in China, where cavernous tuberculosis and chronic osteomyelitis are overly frequent. It seems possible that its frequency could perhaps be explained by the absence of dairy products from the diet. Dairy products are rich in casein, that is, the mother substance from which amyloid may well be formed. Experimentally, amyloidosis develops in animals after feeding of an excess of casein or of casein-rich food, such as milk and cheese. Thus, the absence of casein from the food could well explain the scarcity of amyloid in northern China.

Final Remarks

The disadvantages of the food customs of impoverished Orientals have been emphasized in Western medical literature. The low-protein, low-caloric diet increases the spread of tuberculosis, decreases the resistance against most communicable diseases, favors the development of liver cirrhosis, transforms anchylostomiasis from a relatively harmless infestation to a dangerous disease. All this certainly clamors for correction and improvements. Nevertheless, the Oriental may also ponder the desirability of radical changes of the diet in the United States where, due to nutritional influences, so much gout, serious diabetes, obesity, gall stones, renal stones, amyloidosis, and premature coronary

sclerosis occur This might sound preposterous to our ears, but only because most people are adamant as far as their food preferences and aversions are concerned No nation is willing to concede that its national diet may be lacking in certain important ingredients The Occidentals are just as proud of their blatantly excessive food intake as the Orientals are of their semistarvation diets Since it is easier to find fault with others than with ourselves, one word about the attitude of the Orientals toward well-intentioned western dietitians may be in order

In China, the food customs and ways of preparing food are centuries old. The Chinese pride themselves on the fact that all the different ways in which food is prepared in the Western world are derived from their culinary art In the early Middle Ages, the chief ways of preparing food in the Occident were limited to the baking of bread and the roasting of meat over an open fire At that time, many centuries ago, the Chinese already used the same kitchen techniques they employ nowadays Marco Polo, having learned the art of cooking in China, divulged his knowledge to the Europeans. The Chinese are convinced that their Occidental pupils still have much to learn, and that the Chinese way of preparing food is far superior to the techniques used in our part of the world In their opinion, only the French cuisine approaches their own in excellence In addition, the Chinese often touch slightly upon the fact that, centuries ago, when our ancestors handled their food with their fingers, the Chinese already used chop sticks Marco Polo, upon his return to Italy, devised the first fork which, in the beginning, had only two prongs, hereby clearly showing its derivation from the Chinese chopsticks

All this information may shed light upon the lack of influence which our well-intentioned nutrition specialists have had upon the nutritional preferences and aversions of the Orient Their best propaganda speeches for more modern approaches to the prevention of famine, the balance of diets, *et cetera*, have come to naught when the Oriental smilingly remembers the excellent cooking and refined table manners of his ancestors in the same centuries when the forebears of the "know-it-all" nutritionists still behaved like barbarians

Be this as it may, bitter experiences have taught that it is sometimes even dangerous to tamper with native food customs Many years ago, western nutritionists imagined that they had found a solution for the semistarvation of the population of certain rice-eating regions Rice is a difficult product which requires fertile soil The nutritionists therefore advocated that the cultivation of rice be replaced by that of another carbohydrate product less exacting as far as the quality of the soil was concerned.

In certain Oriental areas, the staple food consists of flour of the Cassava (known also as Manioc or Tapioca), a tuber which can be grown on poor soil unsuitable for rice Another attraction of cassava is its high yield Eight tons of cassava are raised on the same area from which one ton of rice can be harvested Finally, cassava needs little care. As compared with rice, which requires continuous supervision, cassava is a lazy man's harvest. The combination of these characteristics probably explains why the use of cassava as a nutrient is widespread, not only in many parts of the Orient, but also in certain regions of Africa and of South America. Unfortunately, cassava has many dis-

advantages The tuber usually contains considerable traces of hydrocyanic acid, which have to be removed by washing the flour carefully before it is dried This washing carries away most of the protein and vitamin content, low to begin with, of the cassava roots Thus, the protein content of cassava flour does not exceed 1 to 2 per cent; the fat, 0 2 per cent, while the mineral and vitamin contents are negligible

In Africa and South America, the cassava-eating population supplements its carbohydrate diet with small animals caught in the woods Some of the additions to the flour diet (for example, lizards, worms, spiders, other insects, *etc*) are not appetizing to a population not accustomed to these supplementary food articles All this must be considered in order to understand the unfortunate sequence of events when cassava culture was warmly propagated in Java as a solution to the difficulties of nutrition in the less fertile areas Unfortunately, this cassava campaign succeeded only too well, and eventually the cassava harvest of Java was so large that about 200 kilograms of this dangerously poor tuber (70 per cent of which is water) were available per year per capita Thus the cassava areas of Java, where the protein intake often goes down to 20 grams daily per capita, became regions where hypoproteinemia, hunger edema, and other nutritional deficiencies became endemic This result should be a warning to nutritionists not to interfere too readily with native food customs

In the eastern part of the Indonesian Archipelago, *i e* , in the Moluccas and [illegible] lation Sago flour is [illegible] ow is first washed and [illegible] contains practically [illegible] and vitamins The [illegible]

the marrow of a living sago palm, and afterward the opening through which the maggots are introduced is closed with mud Every morning the Papuan auscults the inoculated area Only when the noise of the growing maggots is loud enough is the tree opened again The large maggots are eaten as a delicacy As long as these tribes remain in the virginal forests, their health is relatively satisfactory As soon as civilization teaches these natives to despise the animals of the forest, deficiency diseases appear

[illegible] foods are

toms of primitive peoples indicate that even the human race has not completely lost the instinctive ability to choose food wisely The question might be posed

whether our complicated modern civilization has not harmed the inborn correct nutritional instinct. Too much enthusiasm for certain nutrients has perhaps been originated by well-meaning nutritionists on insufficient experimental evidence

Through television programs, scientific forums may wrongly persuade laymen that interesting scientific problems still under discussion among experts have already led to hard and fast conclusions Clever advertising by large concerns may favor undesirable food preferences. Thus, we Occidentals may well have lost sight of the correct perspectives of nutrition. Perhaps we should avoid preaching to the rest of the world that we have found the final well-balanced, nutritious, and healthy diet. Perhaps we should not try to persuade others to imitate our craving for an excessive intake of calories, proteins, fats, carbohydrates, minerals, hormones, and medicaments.

A STUDY OF HUNGER AND APPETITE IN A YOUNG MAN WITH ESOPHAGEAL OBSTRUCTION AND JEJUNOSTOMY*

By Franklin Hollander, Herbert A. Sober,† and Joseph Bandes
Gastroenterology Research Laboratory, The Mount Sinai Hospital, New York, N. Y.

The work which I am about to report was designed initially to study the influence of actual nutritional intake on hunger and appetite in a human sham-feeding subject, in whom alimentation could be controlled both qualitatively and quantitatively—independently of what the subject ingested orally. Such a dissociation of true and sham feeding presented itself in the person of a young man (identified as Eddie) with an almost completely obstructed esophagus and a surgical jejunostomy for alimentation. Because of a persistence of his desire to eat ordinary foods, even though they were soon regurgitated from his esophageal sac, this individual offered a unique opportunity to investigate the influence of nutritional intake on hunger and appetite *apparently* uncomplicated by (1) the variable gastric distention factor and (2) abnormal influences from the central nervous system. Following attainment of our first objective, a second phase of the investigation was planned to include eating responses following the administration of chemical agents of dietary and pharmacological character. About this time, however, the subject started to manifest marked emotional disturbances, and his eating behavior changed so radically that a new, unanticipated phase of the investigation was initiated.

Clinical Description and Management of the Subject‡

The subject was an ambulatory white male, 18 years old, who was employed in our laboratory specifically for this work. Dysphagia, first noticed when he was 14 years old, developed progressively to the point where regurgitation during meals became a usual occurrence, and one and one-half years later he came to operation at our hospital. At this time a tumorlike ring of the lower end of the esophagus (5 cm. long, hard, nonmalignant), which included the cardia, was excised with transection of the vagi. Continuity was restored by anastomosing stomach to esophagus. In spite of this operation, Eddie continued to regurgitate substances taken by mouth, and two weeks later a jejunostomy was performed for intestinal feeding. Dysphagia and esophageal regurgitation persisted, so that Eddie was completely dependent on jejunal feedings for maintenance of life. His diet consisted chiefly of soups, pureed vegetables, and a "baby-food mixture" of cereal, protein hydrolysate, eggs, milk, etc. These domestic preparations, administered rapidly five or six times a day, were inadequate for the maintenance of body weight, which dropped to a low of 70 lbs

* Preliminary reports of this work were presented before the American Physiological Society in 1950 and the American Gastroenterological Association in 1951.
This paper describes a research undertaken with the support of, and in cooperation with, the Quartermaster Food and Container Institute for the Armed Forces of the United States and has been assigned the number 343 in the series of papers approved for publication. The views or conclusions contained in this report are those of the authors, and are not to be construed as necessarily reflecting the views, or having the endorsement, of the United States Department of the Army.

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‡ Many clinical and experimental details of importance, omitted from this report, have been described elsewhere.

Continuing decline of his nutritional condition on home feeding necessitated repeated readmission to the hospital. On the sixth admission, our laboratory was asked to take over the problem of Eddie's nutritional rehabilitation. He was immediately placed on a predigested synthetic jejunostomy aliment which we had previously devised for the routine care of similar patients Exaggerated hunger disappeared in a few days but thirst reactions subsided more slowly. Bowel and kidney functions also became normal in a ...

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...xcept for a short time at home, initially, his jeju-
nal feeding regime entailed the drip-wise administration of the Jejunostomy Aliment, the nutritional adequacy of which had already been confirmed in other hospitals Written records, in minute detail, of the amounts of the various substances ingested outside the laboratory were brought in by the subject every Monday morning These records, as well as ...

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...daily input of aliment was given in four equal feedings, each lasting about an hour and spaced about an hour apart Variations in daily caloric input were effected by changes in caloric density of the aliment, thus keeping the total volume constant ...

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...provided the interval between feedings was great enough Food taken orally was regurgitated without discomfort, usually about 10 minutes following ingestion Repeated radiographic examination indicated that solids could not enter the stomach, and the amount of fluid which

passed on could hardly transport enough nutrient to influence the results of this study.

For purposes of analysis, the 83 weeks of the investigation have been divided into ten periods, according to the contingencies of the situation

Observations

[illegible]

of the week, starting with, first, the ward period and, subsequently, period I During the ward period, the immediate objective was the physical rehabilitation of the patient and assessment of his suitability as a subject for the proposed investigation During the 12 weeks of this period, *J* was increased gradually from 2,000 to 3,000 Kcal The adequacy of this supply for Eddie's tissue needs was confirmed by the trend of his weight curve, which rose from 80 to 101 lb (Our estimate of the subject's optimum body weight was 125 to 135 lb, and

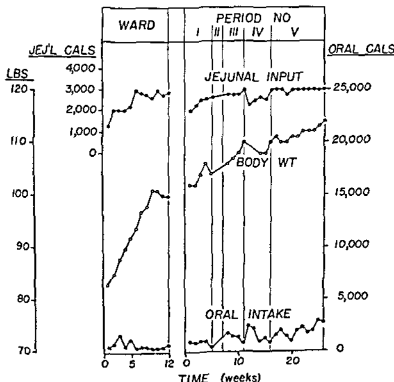


FIGURE 1 Week by-week trends for oral intake, jejunal input, and body weight in sham feeding subject Eddie (ward period and laboratory periods I to V) "Oral cals" represents the weekly average of the number of kilocalories eaten in 24 hours, "Jej'l cals" and "Body wt" represent similar averages of daily measurements

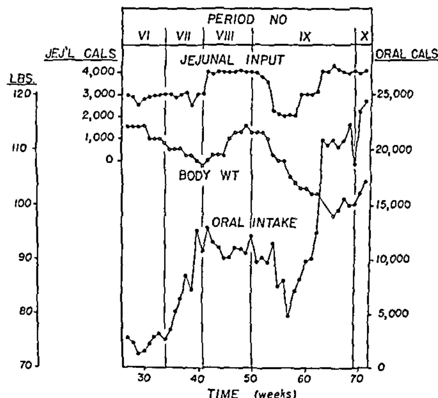


FIGURE 2 Week-by-week trends for oral intake, jejunal input, and body weight in sham-feeding subject, Eddie (laboratory periods VI to X) "Oral cals" represents the weekly average of the number of kilocalories eaten in 24 hours, "Jej'l cals" and "Body wt" represent similar averages of daily measurements

his caloric requirement for maintenance at equilibrium, based on the National

tirely satisfactory as a subject for our purpose, particularly since he gave no evidence of "nervous eating" or any significant abnormality of appetite. He

in J on O. During the five weeks of this period, J increased 38 per cent from an initial value of 1,950 to a final value of 2,640, while O decreased 48 per cent from 1,210 to 630 Kcal Body weight responded favorably, rising to as high as 116 lb When J and O are plotted against each other directly (FIGURE 3), the

relation between O and J must be considered spurious, unless it can be confirmed by an experiment in which O and T are not significantly correlated.

Before this experiment could be attempted, however, the investigation was interrupted at the end of week No. 5 by the discovery that Eddie was in possession of a large supply of barbiturate capsules which he had taken during his early admissions to the ward as a patient. According to his story, he had taken two to five of these capsules practically every day since he came under our observation, which may account for the marked lethargy mentioned above.* Prompt deprivation of these capsules, including those hidden at home, was followed by two convulsive episodes, both of which could be ascribed only to the precipitate interruption of his addiction. He was immediately placed on a course of treatment involving administration of phenobarbital and Dilantin in progressively diminishing dosage, and there were no further repetitions of the convulsions at any time thereafter. Two weeks following discovery of this barbiturate addiction, Eddie was judged to be in a condition suitable for continuation of the study.

During the combined periods III and IV (nine weeks' duration), the objective of the first period was continued. While J was changed irregularly between 2,300 and 3,000 Kcal, O varied between 800 and 2,500 Kcal. This time (FIGURE 3), the correlation between O and T was insignificant ($r = -0.24$) but that between O and J was even higher than in period I ($r = -0.76$).† Hence, it may be concluded that the rectilinear correlation between these latter variables is entirely valid. These data afford an excellent demonstration of the quantitative interdependence of the desire to eat and nutritional intake of calories under the conditions characterizing this investigation. Certain characteristics of the data in periods III and IV, relative to those of period I, should be noted. From the scatter diagrams of FIGURE 3, it is evident that both the slope and the magnitude of the O values are distinctly lower in the earlier of these periods than in the later ones. This difference may be ascribed to Eddie's generally depressed state in period I, and its disappearance after withdrawal of the barbiturates. This interpretation, however, requires independent confirmation.

It was next thought to confirm the interrelation of O and J in another manner, by holding J constant and observing a similar invariance in O. Accordingly, for the next 10 weeks (period V), J was maintained at 3,000 Kcal (except for week No. 19, when it was slightly less). Contrary to expectation, however O varied irregularly between 1,500 and 3,200 Kcal (FIGURES 1 and 3). Although the oral intake is not closely correlated with T, there is some suggestion of a general upward trend of O with time. In fact, all nine of the O values corresponding to $J = 3,000$ Kcal are markedly higher than the two analogous values for the 11th and 16th weeks and for the last two weeks of period V (Nos. 25 and 26), O reached a new high. Several of the individual daily values even

* Subsequently (May 1951), Eddie confessed that he had filched these capsules while still a patient on the ward because he liked to take them, at first to help him fall asleep and later because it was "like taking a couple of drinks." As he became habituated he took them with increasing frequency, sometimes as often as every hour during the day, according to his statement.

† Note that the two points for the 14th and 15th weeks are markedly out of line with the others. If these two were omitted from the statistical calculations, the remaining seven points would have a correlation coefficient of -0.97. No reason is apparent for this divergence of two points out of a total of nine, except that it may be taken as an early sign of the disturbance which manifested itself in the later periods.

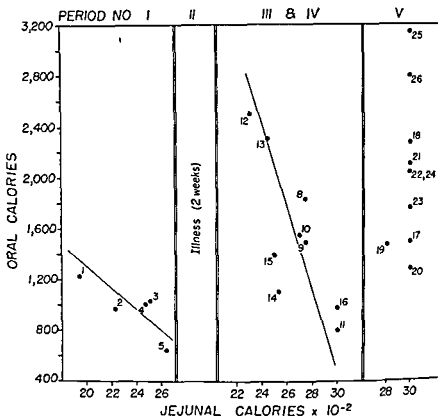


FIGURE 3 Relation between jejunal input and oral intake in sham feeding subject, Eddie (laboratory periods I to V) "Oral calories" and "jejunal calories" represent the weekly averages of the respective measurements made each day in terms of kilocalories The numerical designation of each point represents the number of weeks following transfer of the subject to the laboratory

passed the 6,000-Kcal level. In spite of this discrepancy in Eddie's eating response, his body weight continued to increase, as one might expect it to do at a nutritional input consistently above 2,500 Kcal/day. The failure of Eddie's oral intake to remain reasonably constant while jejunal input was fixed confused the simple picture developed during the previous periods Two alternative explanations for this discrepancy in our observations suggested themselves Either the inverse correlations of the earlier periods still were spurious, for reasons not apparent to us, or else the mechanism for regulating Eddie's oral intake to nutritional need had suffered some kind of a disturbance, also for reasons not

or the reports from his mother gave any support to this explanation at the time

Because of this unexplained inconsistency in the pattern of Eddie's desire to eat, it was decided to devote the next period merely to watching the subject's

behavior, oral and otherwise. This observation was maintained for the eight weeks of period VI, during which *J* was varied between 2,500 and 3,000 Kcal. Even though nutritional supply was invariably adequate for maintenance, according to our estimate, body weight remained constant at 114 lb for four weeks and then declined to a low of 111 lb for the rest of period VI. Oral intake continued to behave in an irregular way, appearing to drop while *J* was being reduced, and to rise while *J* was being increased or held constant (FIGURES 2 and 4). As in the previous period, evidence of a mild degree of hyperorexia continued, the highest single daily value for *O* being 5,920 Kcal. The occurrence

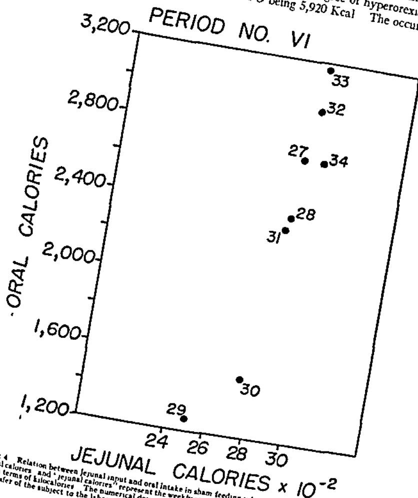


FIGURE 4. Relation between jejunal input and oral intake in sham feeding subject, Eddie (laboratory period VI). "Oral calories" and "jejunal calories" represent the weekly averages of the respective measurements made daily in terms of kilocalories. The numerical designation of each point represents the number of weeks following transfer of the subject to the laboratory.

of depressions and a refusal to cooperate likewise was noted, possibly with a little higher frequency than before.

daily allotment of the jejunostomy aliment. Simultaneously, the mean oral

6,500 Kcal Liver administration was then stopped, but O increased further to 8,500 Kcal for the 38th week, after which it dropped to 7,500 for the second week after liver feeding (No 39) and then rose to 13,000 and 11,000 Kcal for weeks Nos 40 and 41 respectively The over-all trend curve for this period is included in FIGURE 2, the scatter diagrams in FIGURE 5.

had persisted for one week after cessation of the supplement, as might be expected However, the prolongation of the hyperorexia, with only minor recession, for four weeks after stoppage of liver supplement, casts considerable doubt on the validity of this inference Such suspicions are enhanced by (1) the enormous height which the oral intake curve attained toward the end of this period, (2) the evidence of disturbances in the pattern of Eddie's eating behavior which had been accumulating during the preceding period, and (3) the fact that his weight curve was still dropping in spite of a fairly steady jejunal input of 3,000 Kcal/day It was therefore decided to resume the study of jejunal caloric influence and to repeat this liver experiment only after several months had passed (see period X)

Because Eddie's body weight had been falling since the middle of period VI, the next period (VIII) was devoted to bodily rehabilitation, and J was kept at 4,000 Kcal throughout During the first four of these nine weeks, O decreased

periods. Once again, the data failed to conform with the inverse relation of periods I to IV Eddie's appetite had grown to bulimic proportions, and had continued so for several months with only one minor recession On the other hand, his weight curve had now reversed its downward trend, and actually reached its previous maximum of 114 lb., near the end of period VIII. This upward change may simply have been forced by the high level of alimentation, except that this indication of nutritional improvement was being accompanied by a slight recession in eating propensity and, apparently, in the emotional upset as well. Hence, although we cannot state with confidence that body weight

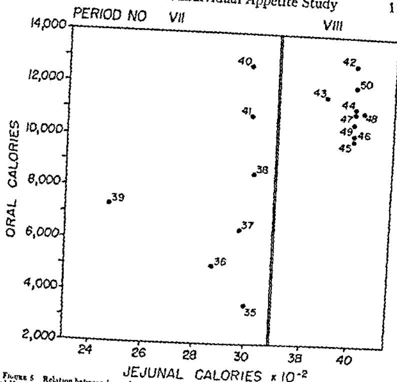


FIGURE 5. Relation between jejunal input and oral intake in sham feeding subject, Eddie (laboratory periods VII and VIII). "Oral calories" and "jejunal calories" represent the weekly averages of the respective measurements made each day in terms of kilocalories. The numerical designation of each point represents the number of weeks following transfer of the subject to the laboratory.

had been responding to the same disturbing factor that was influencing appetite, the possibility is certainly latent in these observations, and [illegible]

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more th[illegible],000, while jejunal input was once more about 4,000 Kcal/day.

* A repetition of the experiment with whole liver substance was conducted near the end of this confined period, but the over-all pattern of eating behavior again deprived this effort of all significance, and its details are omitted from the body of this paper.

Eddie was now eating almost incessantly, and his emotional status had reached such a state that he and his family were forced to take action in regard to therapy, and our experimental study was discontinued.

Throughout the ward period and periods I to IV, Eddie and his mother were greatly distressed about his physical condition, but they resisted all suggestions regarding further surgery for its relief. However, his conversation and behavior during the first four months in the laboratory indicated a gradual adjustment to his physical abnormality and his role in the experimental situation. Anxiety concerning his current or future status was evinced only on rare occasions, and never was excessive. Although Eddie was generally highly emotional, nervous and superstitious, we were not aware of any current psychiatric

group He cultivated his old friends once more, joined a club, played an accordion in a band, went to ball games and prize fights, attempted roller skating occasionally, and even went to eat in public places with companions of both

the masticated food

came depressed, morose, and cranky, and even threatened to stop coming to the laboratory His cooperation became very poor, and he frequently refused to

from a series of
riends taunted
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being and his dependence on "baby food." The presence of girls in the group, and his failure to attract one of them to himself because of his abnormality, evidently added to his troubles In general, Eddie was passing through an exceedingly difficult adolescent period

Unequivocal evidence of bulimia came about the 40th week (in period VII), when the increase in appetite accompanying the addition of liver to the predigested aliment failed to disappear within a reasonable time after discontinuance of the supplement From then on, Eddie was truly voracious, and he often remarked that he "simply could not satisfy his hunger." On some days, hyperorexia was relatively mild, often it diminished during his stay in the laboratory, and became overwhelming only after he went home at night. On other days, he ate almost incessantly, even during jejunal alimentation. More than once, the reports from his mother revealed that he continued eating until after midnight, when he finally fell asleep, only to awaken several hours later to start all over again

The emotional basis of this bulimia was evident from many of the casual re-

[illegible]

things" and, on the occasion of one of his not infrequent arguments with her, he reported that such conflicts always made him hungry. On another occasion, his mother reported that "nothing satisfies his hunger—and we have had no upsets of any kind"

[illegible]

at home In addition, about this time, there appeared a couple of newspaper reports from distant parts of the country about cures of other individuals with esophageal obstruction, and pressure from relatives and neighbors to do something about Eddie's condition became overwhelming During the last weeks of the investigation, his eating was so violent that he often became physically exhausted by the continuous insertion of food into his mouth and its almost immediate regurgitation until, as described by his mother, he became "half unconscious." Finally, in the middle of a work day, he abruptly left the laboratory and the investigation terminated, 83 weeks after the beginning of the Ward Period.

During the next six months, Eddie was taken from one hospital to another in search of nonsurgical relief, in spite of our judgment that only surgery offered any promise of help. At each clinic he was told that his condition was essentially psychosomatic, contrary to our opinion, and surgery was denied him Finally, he came back to this hospital, was operated on by the chief of one of the surgical services, and was restored to a normal way of life, including the acquisi- [illegible]

Discussion

Let us stop to summarize this situation At the outset, this project was designed to be a study of the influence of the alimentary supply of calories and certain specific dietary factors on Eddie's desire to eat The popular concept that hunger and appetite are repressed by feeding and augmented by fasting, has its counterpart in statements such as that of Harte and his associates[4] that "the primary ... of food is the satisfaction of energy require- [illegible] he appetite of the [illegible] " Nevertheless, [illegible] negated, *e g*, the hyperorexia associated with obesity, and anorexia nervosa with its attendant cachexia. Such contrary phenomena heighten the fact that decisive quantita- [illegible]

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ject in whom the usual influence of a variable distention factor on the desire to eat and evident psychological abnormalities related to oral behavior were both absent.

The results of the first four periods of the investigation afford evidence of a first principle in eating behavior; namely, *that component of the desire to eat which is initiated by metabolic needs of the body varies inversely with the caloric intake*, under the restricted conditions characterizing the early part of this study.

with a considerably wider range of jejunal input, this relation would probably have been found to be curvilinear. The variability of oral intake with fixed

16th week As a result of this new factor, all evidence of the operation of this chemiconutritional control was obliterated The possibility was entertained that Eddie's abnormal appetite might have resulted from nutritional need rather than a psychological disturbance. Evidence against this conclusion is as follows: (1) the bulimia was manifest even at a time when body weight was between 108 and 114 lb, which is not a great deal less than the maximum ever

perorexia was purely oral and was never accompanied by a desire to ingest ex-

by a mounting emotional disturbance; and, finally (5) following the successful corrective operation, bulimia has never again been manifest. Hence, the results of the latter half of the investigation afford conclusive evidence of another major principle in eating behavior: namely, *there exists a second component of the desire to eat which is activated solely by neural processes*, frequently but not invariably involving emotional reactions. This component of eating behavior, which may be designated as "eating for the sake of eating," can operate almost incessantly in man in the absence of the inhibiting action of gastric distention. This second principle, well demonstrated by the pathological manifestations in Eddie, may be identical with the similar one adduced from the canine evidence reported by Doctor Janowitz,[6] and both may be activated through the hypothalamic mechanism discussed by Doctor Brobeck.[7]

That part of the investigation which dealt with the influence of whole liver substance focuses attention on a third basic principle: namely, *the desire to eat can be augmented or diminished by individual chemical substances, nutritional or pharmacological, even in the absence of overt caloric need.* Unfortunately, the results on this aspect of our study were confounded by the bulimia, and even a repetition of the experiment contributed nothing reliable on this point.

The nature of the psychophysiological disturbance in eating behavior could not be established in our Psychiatric Clinic during the course of the investiga-

40,000 or more kilocalories in a single day, presents a fascinating and most important problem—relative to the purely neural component of eating behavior

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7 BROBECK, J. R. 1955. Ann N Y. Acad Sci 63(1): 44–55

Discussion of the Paper

DOCTOR LEON MOSES (*College of Physicians and Surgeons, Columbia University, New York, N.Y.*). Doctor Hollander has asked me to make some comments [illegible] He is

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subject's emotional motivations or mood states It is most unfortunate that *it was not possible* to obtain detailed psychodynamic data *during these most*

[illegible]

The following *tentative design of a human* [illegible] may help solve this problem. This scheme was found useful in an intensive psychoanalytic and ballistocardiographic investigation of cases of essential hypertension. At present, it is also being applied to the experimental study of peptic ulcer.

Design of a Human Psychophysiological Experiment

A *Selection of Medical Case*

Transient phase, sustained phase, complicated phase

B *Selection of Associated Psychiatric State*

Character disorders, anxiety states, severe neurotic states, psychotic states

C *Physiological Techniques for Correlative Studies*

(1) [illegible]

D *Psychological Techniques for Correlative Studies*

(1) Psychoanalytic investigations are best conducted in the life situation.
(2) Appreciation of the meaning of the investigative procedure on the patient and its effect on the flow of unconscious material, the transference reaction and the psychotherapeutic changes
(3) Duration of study
For qualitative psychodynamic patterns 50 to 100 sessions
For quantitative psychodynamic patterns 300 to 500 sessions.

E *Psychotherapeutic Reversal of the Pathophysiological State*

F *Statistical Significance of Data*

(1) *Individual Case Control* 3 to 5 years of a continuous pathophysiological state prior to therapy and 3 to 5 year follow-up remission
(2) *Significant Statistical Sample Group*
[illegible] sessions) or a more intensive psychoanalytic treatment

With such combined investigations, the psychological state of the human experimental subject need no longer be the "uncontrolled variable"

CLINICALLY USEFUL APPETITE DEPRESSANTS

By Stanley C Harris

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Apparently the obesity resulting from increased food intake and its jeopardy has been recognized since antiquity. Bruch[1] quotes Durant in stating that the ancient Cretans had an "ideal drug"—one that permitted a person to eat as much as he liked without gaining weight.

A few compounds have been used in more contemporary times, which, by metabolic stimulation, approach the so-called ideal drug mentioned above. Dinitrophenol for the treatment of obesity, by increasing metabolism, was introduced in 1933[2,3] Its toxic side effects, however, mitigate against its use for this purpose, according to the Council on Pharmacy and Chemistry of the American Medical Association, 1935[4]

Extract of thyroid has long been used to facilitate weight loss in the obese Current literature seems to agree that, unless the patient actually has hypothyroidism, the drug should not be used The hazards exceed the benefits, and it is even possible that weight gain be associated with thyroid therapy

The early work of Benedict[5] on calorimetry and, more recently, of Newburgh,[6] clearly show that the physical laws of conservation of energy apply to body weight problems It also becomes clear from their work that it is much easier to avoid calor [illegible]

h.

weight is the result of caloric absorption in excess of caloric expenditure It must follow, therefore, that good therapeutics require that methods for inducing reduction of body weight should be directed at the cause rather than the symptom

It appears, however, that the personality problems of the majority of obese patients are such that time-consuming psychotherapy is necessary to rectify or control the basic cause of excess appetite By way of a compromise, the profession has come to use anorexigenic drugs to treat the abnormal appetites, which is treating the symptom of the basic cause, not the cause of the obese symptom.

Some of the belladonna preparations have been used to inhibit appetite, apparently by causing loss of pleasure in eating Another effort at drug-induced anorexia has been described by Gould,[7] who claimed that a mixture containing benzocaine and flavoring extracts helped his patients reduce No placebo treatments or other controls were described

The use of sympathomimetic drugs as appetite depressants began with the observations of Nathanson,[8] Davidoff and Reifenstein,[9] and Ulrich,[10] who noted weight reduction as a side effect in patients under amphetamine treatment. Lesses and Myerson[11] and Rosenberg[12] were among the first to report the successful use of amphetamine in the clinical management of the obese

Their reports were follo[illegible]

[illegible]

Minkowski,[35] on rats

Some effort was made by the earlier investigators to assign an explanation to this phenomenon, and the following mechanisms were suggested: (1) increased basal metabolism; (2) increased general metabolism; (3) diuresis; (4) incomplete digestion and/or absorption of food; and (5) reduced food intake due to appetite reduction or an associated phenomenon.

A host of authors[9, 9, 10, 13, 14, 15, 36-47] have considered the possible influence of amphetamine upon metabolism, and yet no one has been able to base upon carefully controlled experiments the conclusion that basal metabolic rate is altered Increase of general metabolism, however, seems to be justified Ulrich,[10] Lesses and Myerson,[11] Rosenthal and Solomon,[12] Davidoff and Reifenstein,[9] Foltz, Ivy, and Barborka,[43] Peoples and Guttman[49] have all reported that their patients or subjects reported feeling more like working when receiving amphetamine Rather careful studies on small laboratory animals consistently revealed some order of [illegible] that part of the weight loss might be due to this mechanism.[9, 57, 58, 59] Possible mechan[illegible]ney [illegible]irst

[illegible]

Early evidence, from subjective reports by patients and clinical observations, pointed to decreased appetite as a feature of amphetamine treatment. Acceptance of this concept directed attention to the basis of anorexia. Great is the number who have studied the motor activity (tone and motility) of the gastrointestinal tract after amphetamine treatment.

[illegible] initial activity.

Smith and Chamberlin[62] observed a delay in gastric emptying, but very little effect on gastric peristalsis in four subjects given 20 mgm. of Benzedrine. Generally similar conclusions were voiced by others after human or canine observations[63-69]

Myerson and Ritvo,[61] Smith and Chamberlin,[62] and Elson, Glenn, and Drossner[70] all studied intestinal tone and motility. Experience ranged from no change to some decrease in activity. The latter comment may also be applied to the [illegible] of treats and controls to be the same.

A carefully planned objective study on humans and dogs under laboratory conditions was carried out to elucidate more clearly some of the above expla-

HUMANS on "AD LIB" DIET

FIGURE 1

nations for amphetamine-induced weight loss.[74, 75] When seven obese and two nonobese volunteer subjects were fed three meals a day for two eight-week periods separated by a four-week vacation, 5 mgm. d- or 10 mgm. dl-amphetamine, three times a day one hour before meals, both voluntary caloric intake and body weight were reduced. The accompanying illustrations, FIGURES 1 and 2, reveal the experience.

Similar, but more dramatic, experience was obtained in dogs—2.5 to 5 mgm. dl-amphetamine intramuscularly an hour before feeding substantially decreased food intake (FIGURE 3), the food being removed after 45 minutes. Ten mgm. per day to a 16 kg. dog (dog #3, FIGURE 4) reduced food intake 87 per cent and body weight 27.4 per cent in 32 days.

The behavior of the dogs on being presented with food after being injected with amphetamine was most interesting. They were apparently very pleased that the food had been brought to them even though they would not touch or, at times, even sniff it. They still manifested the usual jealousy at not being the first to be fed. Several of the dogs would look at the food, circle their cages, look at the food, maintain this cycle for several minutes, and then lie down or stand at the cage door wagging their tails, apparently enjoying the

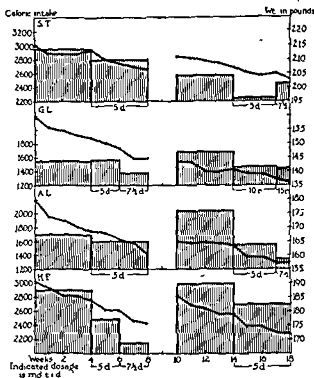


FIGURE 2

presence of the attendant. The injection of saline solution, instead of amphetamine, was followed by enthusiastic ingestion This is important because it shows that, in the dog, the placebo injection, even after 30 days of conditioning with amphetamine, was not a substitute for the anorexia-producing effects of amphetamine. No evidence of revulsion or nausea whatever was observed in the dog series

Having known in advance what the daily caloric requirement was for each of the eight animals in the series to maintain their body weight, and after studying the change in their body weight that occurred after the daily amphetamine administration, it was possible to calculate, according to Benedict's figures, what the anticipated body weight should be at the end of each period of amphetamine inhibition; and, on the basis of such calculations, it was possible to account for all the body weight loss in terms of caloric deficiency of int[illegible]

sp

weight. The same dose of *amphetamine after either or both* surgical procedures modified food intake as before surgery. This experience is interpreted

INFLUENCE of AMPHETAMINE on "APPETITE"

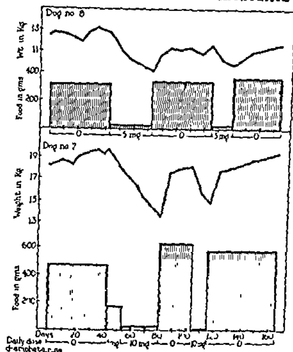


FIGURE 3

to indicate that anorexia is due neither to sensations from, nor stimuli to, the gastrointestinal tract.

To ascertain any toxic or metabolic effects of amphetamine, 10 male volunteers of normal weight were given 3000 calories per day for 14 consecutive weeks From day 27 to 56 inclusive, each man took 5 mgm d- or 10 mgm dl-amphetamine before each meal An average weight loss of 0 7 lbs occurred during the control period (26 days) On medication, the group averaged, during the first week, a loss of 0.9 lb, but the average loss for the entire 56 days of treatment was 1 8 lb, only 0 4 lb less than if the control rate had continued The only interpretation possible is that there was increased total

lb during four weeks of control, 2 97 lb during the first week of treatment, and 3 43 lb during four weeks of medication During the second eight-week experiment, the quantitative results averaged: 2 01 lb during four weeks control; 2.74 lb during the first week of medication, 5 50 lb. during four weeks of treatment.*

* The average initial weight of the *ad lib.* group was 170 7 lb, of the constant diet group, 168 5 lb

EFFECT of INCREASING DOSAGE of AMPHETAMINE on "APPETITE"

FIGURE 4

INFLUENCE of NEURONECTOMY on AMPHETAMINE INDUCED ANOREXIA

FIGURE 5

Urine volumes were determined in the constant caloric intake group. Though water intake was not measured, diuresis evidence did not appear until three weeks after medication had begun, when the rate of weight loss had been reduced

Since all evidence of this study[74, 75] points to anorexia of central origin, eight postfrontal lobectomy patients exhibiting bulimia were given 10 mgm. of d-amphetamine intramuscularly an hour before lunch and dinner on two successive days. The observed reports are summarized as follows

	Number of Cases Eating		Number of Cases With Appetite	
	Normal	Less	Normal	Less
Lunch	8	0	8	0
Supper	8	0	7	0
Lunch	7	1	6	2
Supper	6	2	6	2

The relatively large dose of d-amphetamine (10 mgm) was without effect on the appetite of six of eight prefrontal lobotomy patients with bulimia.

On the basis of the above experience and the literature on the subject, there can be little doubt that amphetamine induces weight loss primarily by facilitating a diet of lower caloric value and, secondarily, by increasing caloric expenditure through voluntary activity. Williams[23] has said that patients lose weight as well without drugs, if they adhere to their diets

[illegible] central phenomenon It [illegible] or attentive to activities other than ingestion remains unanswered

Tolerance to the anorexigenic activity drugs may occur Thoughtful clinicians seem to prefer using the drugs until they are tolerated, hoping to teach the patient new eating habits, though some maintain patients on amphetamines for many months.

Side effects are relatively few. The most common are restlessness and insomnia. The feared side effects are hypertension; though Osserman and Dolger,[28] treating diabetics; Freed,[31] treating obese hypertensives, and Coopersmith,[28] treating overweight pregnancies, all observed blood pressure to diminish as body weight reduced

[illegible] Benzedrine or [illegible]

d 1 phenyl-2-aminopropane (Dexedrine), 1 cyclohexyl-2 aminopropane [illegible] that order He also [illegible] se of d-amphetamine in sustained release form (spansules) They found a single daily dose in the morning, in this form, to act without decrease in efficacy or increase in the incidence of side effects

This, then, is the substance of the information pertaining to clinically effective anorexigenic drugs. *It is clearly established that the amphetamines* facilitate loss of body weight in obese and nonobese humans and in laboratory animals. This effect is achieved principally by reduction of voluntary food intake but, to a small extent, in some cases, by a moderate increase in energy metabolism.

How is "appetite" diminished by amphetamine? In the light of current information, a number of explanations deserve consideration.

(1) Is interference with motor activity of the gastrointestinal tract responsible? In the first place, it seems unlikely that alteration in tone or motility of the gut could modify amphetamine anorexia. In the second place, such changes which have been reported are nominal.

(2) Is blood chemistry altered by amphetamine? We have found no significant changes in blood glucose or glucose tolerance in our human subjects either immediately or weeks after amphetamine treatment. If the arterial-venous glucose difference is affected by amphetamine, the information is lacking. It is conceivable that the peripheral vascular effects of amphetamine might influence such a process, but then, Williams found cyclohexyl amino propane to be almost as anorexigenic as Dexedrine, though it is very much less active as a vasoconstrictor.

(3) Is intoxication responsible for the anorexia? The paucity of reports of disturbed body chemistry or function indicates that amphetamine, in clinically proper quantities, is no more toxic than a good meal, bad news, or a sudden fright.

(4) Is anorexia a necessary product of cerebral excitation? It is true that many eat less when agitated, but so do many who are depressed. The converse is also true. Gelvin and McGavack[21] found Aptrol (2-amino-1-(p-methyl phenyl)-propane to be 1/5 as anorexigenic but 1/20 as analeptic as Dexedrine. Further, many clinicians have found that addition of a barbiturate to amphetamine allays the restlessness and analepsis sometimes seen in patients unaccustomed to the drug without negating the anorexia. A final comment on this point: amphetamine usually induces anorexia, regardless of the patient's temperament. It is interesting to note, in this respect, that 4 to 5 hours after ingestion of amphetamine, many patients become aware of a rekindled desire to eat. It is entirely possible that some degree of tolerance develops to amphetamine-induced anorexia over a period of time, but some of this tolerance may well be due to accrued nutritional deficiency.

(5) Does amphetamine have a psychological effect which affords a patient more self-confidence, hence less insecurity, which Doctor Bruch has said may be causative to the obesity-producing behavior? Perhaps this may be the case. I have seen such effects occur, but the opposite effects are also seen.

(6) Does amphetamine have a specific inhibitory effect upon an "appetite center," or a specific stimulatory effect upon an "appetite inhibiting" center or process? This question remains unanswerable unless Doctor Brobeck has *tested the drugs on some of his ablation preparations.*

That the use of amphetamine for inducing anorexia has been accepted clinically is attested by unpublished information supplied by a large pharmaceutical

manufacturer which estimates that 92 per cent of physicians use amphetamine in treating obesity, and that 65 per cent of patients treated for obesity are given amphetamine.

As a student of pharmacology, I cannot conclude this presentation without a remark about what appears to be the prevailing management of the obese: severely restrict caloric intake and insure patient cooperation by giving an anorexigenic drug I am aware of the fact that the obese patient is a chronic problem who is easily discouraged as he tries to reduce In fact, some clinicians justify the use of diuretics by saying that it increases the rate of weight loss and helps the patient stay on a diet However, since most obese patients become that way gradually, over a long period of time, why not study the diet and caloric intake of the patient, reduce it 10 per cent by judicious substitution according to readily available tables, at no sacrifice of bulk or frequency of eating, and let the patient reduce slowly and comfortably without drugs? Perhaps Coopersmith[25] is correct when he says that if the physician could spend more time with the patients and talk over their problems he would need to prescribe less amphetamine

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THE ACTION OF VARIOUS DELETERIOUS COMPOUNDS ON VOLUNTARY FOOD INTAKE

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Introduction

Deleterious compounds, also widely referred to as inhibitors, may be defined as such only under the conditions under which they act. Many compounds, including essential nutrients, may act as inhibitors or deleterious compounds under certain specific conditions which include the physiologic state of the animal, the composition of the animal, the composition of the diet and the nature of environment in which the animal happens to live.

Food intake is so basic to the survival of the animal that it is to be anticipated that many mechanisms exist to insure its satisfactory operation. Most of these mechanisms are unknown. Interference with any one of them will result in impairment of normal food intake, increasing or decreasing it.

Nutrients absorbed during active digestion are largely converted to fat that is stored in the adipose tissue, from which it is mobilized to meet the energy needs of the animal during the postabsorptive period. Interference with disposal mechanisms will *decrease* food intake, and there will follow an *increase* in food intake when fat mobilization mechanisms are interfered with In the postabsorptive state, when energy is no longer available from the gastrointestinal tract, the tissue cells depend largely upon the depots for the energy they need, so that when the fat mobilization mechanisms are interfered with, the cells enter a state of undernutrition that activates the homeostatic mechanisms regulating food intake, resulting in hunger and an increase in food intake

The functional state of the liver is of special importance in regulating food intake. Subtotal hepatectomy and the injection of carbon tetrachloride into the mesenteric vein reduced the amount of functional liver tissue without causing damage to other tissues Both procedures resulted in a marked anorexia and a profound reduction in the effective motility of the stomach and small intestine. Restoration of liver function was accompanied by a return of normal appetite and gastrointestinal function. This was most likely caused by some humoral process, "a toxic substance normally inactivated by the liver, the lack of some substance secreted by a healthy liver or some more indirect mechanism." [1]

Deleterious Compounds and Liver Function

Any compound interfering with liver function is likely to interfere with food intake Highly unsaturated readily oxidizable fatty acids fed with diets low [illegible] to the liver
[illegible] in-
[illegible] de-

The hepatoxins constitute a large class of compounds that act to cause liver

damage, which is accompanied by decreased food intake Compounds counteracting the deleterious action of the hepatoxins will protect the liver against injury and increase food intake[4] Considerations of food intake must take into consideration a functional liver

Deleterious Compounds and Disposal Mechanisms

Nutritional deficiencies Perhaps the most frequent cause of decreases in food intake is an interference with any mechanism necessary for the disposal of absorbed nutrients. Since nutrients are disposed of by oxidation, synthesis into tissues, deposition of glycogen in the liver and muscles and, most of all, through lipogenesis and storage of the fat in the adipose tissue, any compound interfering with any of these mechanisms will act to decrease food intake Such compounds occur in foods and act by precipitating deficiencies of essential nutrients which are component parts of the enzyme systems that participate in the disposal of absorbed nutrients Impairment of function of such enzyme systems for want of adequate amounts of essential nutrients results in decreased food intake Such nutritional deficiencies occur when

(1) Compounds inactivate, destroy, or interfere with the absorption of essential nutrients Among them are avidin, thiaminase, and linseed meal, which cause deficiencies of biotin, thiamine, and pyridoxine respectively[5]

(2) Metabolic inhibitors of specific nutrients interfere with their utilization and precipitate nutritional deficiencies A great variety of such antimetabolites have been produced synthetically, and they produce deficiencies of essential nutrients[6] Not all metabolic inhibitors are laboratory creations Dicoumarol, the metabolic inhibitor of vitamin K, was found in spoiled sweet [illegible]

pates only in a highly specific function, the maintenance of the prothrombin level in the blood The essential unsaturated fatty acids also seem to have no effect upon food intake,[8] presumably because they do not function in food disposal mechanisms, but the possibilities are by no means ruled out that conditions may exist under which they could very well exert an influence upon food intake

Toxic agents It is frequently difficult to distinguish between toxicity and nutritional deficiency An enzyme system may be impaired by the absence of a coenzyme for want of an essential nutrient that is necessary for its formation or by the interference in the normal function of the protein moiety of the enzyme Thus, pyruvic oxidase may be functionally impaired by: (1) the arsenic of lewisite which inactivates the functional —SH groups of the protein moiety, or (2) by a deficiency of thiamine which is necessary to form cocarboxylase, the coenzyme of pyruvic oxidase "Here a deficiency and a toxicity may lead to the same biological defect, the oxidation of pyruvic acid, even though different components of the enzyme system may be affected"[9]

Composition of the Animal and Deleterious Compounds

Fat content The fat content of an animal may be a determinant of food intake Rats with a normal body-fat content, when presented with a diet diluted with kaolin, will maintain their normal weight and caloric intake by properly increasing the consumption of the kaolin-containing diet. Rats that have become obese as a consequence of hypothalamic injury[10] or mice rendered obese by gold thioglucose treatment[11] fail to make this adjustment. Instead, they decrease their food intake and lose weight. It is a matter of judgment whether kaolin is to be considered a deleterious compound under these conditions

Pattern of enzyme systems Nicotinamide produced a methionine deficiency in rats because it undergoes obligatory methylation before excretion. Methionine seems to be the source of these labile methyl groups, and its deficiency is accompanied by a decrease in food intake[12] There was no methionine deficiency nor a decrease in food intake in guinea pigs and rabbits fed an excess of nicotinamide, since they excrete nicotinamide without methylating it[12] The enzyme systems of the animal thus determined whether excess nicotinamide was innocuous or acted as a deleterious compound

Physiologic State of the Animal and Deleterious Compounds

Nutritional deficiencies Nutrients may behave in an unpredictable way when fed to nutritionally deficient rats In thiamin deficiency, the intake of carbohydrate in free-choice experiments is sharply reduced, while that of fat is increased These effects seem to be the result of the impaired disposal of carbohydrates[13] in thiamine deficiency

Methionine when fed to rats deficient in pyridoxine behaves in a different manner from that in rats deficient in pantothenic acid On a phyridoxine deficient diet, as little as 0 4 per cent methionine depressed growth[14, 15] On a pantothenic acid deficient diet, a similar amount of methionine promoted growth[16] The internal chemistry or physiologic state is an important determinant in the deleterious character of compounds

On nicotinic acid deficient low casein diets, cystine depressed growth When the diet was supplemented with nicotinic acid, typtophane or fat, cystine stimulated growth[17] On nicotinic acid deficient low casein diets supplemented with cystine, threonine depressed growth in rats and thus became a deleterious compound[18] Other studies with chicks have been reported of unpredictable activities of amino acids when fed nicotinic acid and pyridoxine deficient diets[19]

Hormonal imbalances Severe upsets in the internal chemistry by hormonal [illegible]

increase in food intake[20] Here, phosphorus acts as a deleterious compound and has a most profound influence upon food intake by a mechanism that is at present unknown

In adrenalectomized rats, potassium in excess becomes deleterious,[21] further

emphasizing the role of the physiologic state of the animal in determining whether a compound acts as an essential nutrient or as an inhibitor

Composition of the Diet and Deleterious Compounds

Upon diets containing pure amino acids as the source of protein, cystine played little role in food intake while methionine had a marked effect [22] Either methionine deficiency or excess will decrease food intake When fed in amounts two to three times its optimal level, methionine becomes deleterious and depresses food intake by mechanisms that are not at all understood The excess methionine may be counteracted by glycocyamine[23] or increased levels of protein intake in chicks[24] and by molar equivalents of glycine and arginine plus falacin, vitamin B_{12} and vitamin E in rats [25] On the other hand, excess dietary glycine decreased growth and food intake, and complete protection against such glycine toxicity was given by methionine plus vitamin E [25] Methionine interrelationships seem to be quite complicated

Nonspecific Deleterious Compounds

Many compounds depress food intake in a manner that is not understood Among them are gossypol[26] and the alfalfa inhibitor, saponin [27]

Rancid fats depress food intake They may do so by destroying vitamins,[5] by increasing protein requirements[28] or by acting in some as yet undetermined manner

Pesticides which are finding progressively increased use in food production and storage may affect food intake in various ways Their effect upon the flavor of foods[29] deserves serious consideration Pesticides may affect enzyme systems without appreciably affecting food intake "It has been demonstrated with several of these agents that gross effects such as retardation of growth and normal activity, may not occur at absorption levels which produce significant tissue damage "[30] On the other hand, diets containing 250 p p m of parathion will completely stop the food intake of rats so that they die of starvation [31]

Pyrogens

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INTERPRETATION OF FOOD INTAKE DATA OBTAINED IN CHRONIC TOXICITY TESTS

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Although metabolic studies accounting for 100 per cent of administered chemicals or drugs are desired and sought after, it is believed that chronic toxicity data will usually be necessary to establish "Proof of Safety"[1] The metabolic products may be completely accounted for, but toxicity could possibly be inherent in the actual metabolism

In undertaking chronic toxicity experiments, it is usually planned to measure the growth of the animals along with their food, water, and drug consumption with observations on well-being and longevity during the test[2] Albino rats are the most common animals used in this work because of their low susceptibility to infectious diseases Other species, however, may prove useful in this work It has been found that 10 rats on each dose level supply enough data for adequate statistical treatment when environmental conditions are kept constant Usually five animals are kept together in standard oblong cages with water always available A diet as completely adequate as possible should be used unless specific metabolic studies are planned, with results to be interpreted accordingly, as in the study of emetine toxicity in rats[3]

The material under test is usually incorporated in the diet This mode of administration is advantageous because the drug is continually available and is not accompanied by a trauma, as when given by intramuscular injection or even by stomach tube, both of which methods produce an even more acute effect Interpretation of the data obtained must be done with extreme care, emphasis being placed on logical explanations of deviations from control values Experience of the investigators is of immeasurable value in conducting and evaluating chronic toxicity tests As Doctor Lepkovsky[4] has pointed out, many biologically active compounds play a role in modifying food intake and, as yet, their actions are only partially understood It should be emphasized that temperature changes affect the food and water consumption of animals[5, 6] Sex also is important in regulating food intake,[5, 6] and the results for males and females should be recorded separately Adequate controls are most important

It is obvious that taste may limit the animals' acceptance of food to which a bitter tasting material has been added It must be admitted, however, that the taste threshold of animals may be different from that of humans, and that materials having a desirable taste to humans may be less desirable or nonde- [illegible]

[illegible]

average food intake over a 28-day period was 12 0 grams per rat per day However, when 12 5 grams of quinine sulfate was incorporated in each kilogram of diet, the daily intake decreased to 5 4 grams per day with resultant

TABLE 1
SUMMARY OF FOOD INTAKE DATA

Drug administered	Food intake, gm per day	Average starting weight, gm	Average final weight, gm
0	0 (Starvation)	47 2	30 2 (Average length of life—5 5 days)
0	2 0 (Semistarvation)	47 4	32 7 (Average length of life—22 5 days)
Controls	12 0 (*ad libitum*)	56 6	155 7 (28 days)
Saline—I P	12 6 (*ad libitum*)	49 8	151 1 (28 days)
Quinine sulfate, (12 5 gms /kg diet)	5 4 (*ad libitum*)	57 8	65 2 (28 days) (3 deaths)
Quinine sulfate (1 0 gm / kg body wt /day by stomach tube)	8 8 (*ad libitum*)	52 3	106 0 (28 days) (5 deaths)

TABLE 2
RESULTS IN THE CHRONIC TOXICITY TEST OF 'KEMADRIN'

Dose	Length of test	Average starting weight, gm	Average final weight, gm	"t" Compared with controls	Average gain, gm	Total food intake gm /rat	Total drug consumed	
							mg /rat	mg /kg wt /day
Controls	28 days	48 5	184 5	—	136 0	365	—	—
1 25 gm /kg diet	28 days	48 6	159 4	4 43*	110.8	298	372	83
Controls	84 days	48 5	309 5	—	261 0	1,321	—	—
1 25 gm /kg diet	84 days	48 6	292 6	1 28	244 0	1,201	1,502	61

* Significant at P = 05 level

mpaired growth Three of the 10 rats died before the end of the 28 days In contrast, when the quinine was given by stomach tube in the same amount of 1 gm /kg body weight per day, the food intake decreased only to 8 8 grams per rat per day (TABLE 1) The thick suspension of the drug was very difficult to administer by tube at this high dosage level, and 5 of the 10 animals died before the end of the 4-week period due to the fact that small amounts of the drug had entered the lungs More data on this type of comparison have been presented by Smith[7]

The fact that three animals died when eating the quinine diet introduced the question of length of life during starvation and semistarvation It was found that when no food was given (water *ad libitum*), the 22-day-old rats lived, on an average, only 5 5 days longer, dying between the 4th and 7th day. When 2 grams of food were given each day, the length of life was increased by 22 5 days, the animals dying between the 16th and 25th days on test

Another bitter-tasting drug, Kemadrin,* at a dose level of 1 25 grams per kilogram diet, decreased food intake for the first month the animals were on test but, after this period of adjustment, the food intake and weight gains were

* 'Kemadrin' brand 3 Pyrrolidino 1 phenyl 1 cyclohexylpropan 1-ol hydrochloride Burroughs Wellcome & Co , London, England

TABLE 3

*RESULTS IN THE 84 DAY CHRONIC TOXICITY TEST OF 'DAREPRIM'**

Drug administered mg /kg diet	Average starting weight, gm	Average final weight, gm	Fiducial limits 2 × s E	Gain, gm	Total food consumption gm /rat	Drug consumption mg /kg body weight/ day
800	48 0	187 2	±15 8	139 2 (1 death)	946	48
400	47 9	216 8	17 2	168 9	1064	24
200	48 4	242 6	19 0	194 2	1175	12
100	48 7	255 1	22 8	206 4	1232	6
Controls	47 2	259 8	23 4	212 6	1257	—

* From the values obtained in this test the highest dose of 800 mg /kg diet may be said to be definitely toxic, while the 400 mg dose is on the borderline of being considered toxic during this 84-day period

not significantly different from those of the controls (TABLE 2) Duration of tests, therefore, must be given proper consideration in evaluating data

Intraperitoneal saline injections made twice a day with a No 26 hypodermic

The evaluation of anorexiant drugs in animals is an extremely difficult task It has been shown by Tainter[8] that 5 mg to 15 mg per kg body weight per day of amphetamine was necessary to depress the food intake of rats temporarily These amounts are approaching toxic values and, when compared to prescribed human dosages, are rather large, but more drug may be required in animals whose usual activity and metabolism is much higher than that of humans, and whose food intake is about 10 to 12 per cent of body weight as compared to 3 to 4 per cent for humans

An easily interpreted chronic toxicity test would be one in which a tasteless drug, incorporated at different levels in the diet, would produce different amounts of food intake and different lengths of life after appropriate quantities of the diet have been eaten The chronic toxicity test of Daraprim* is an example of such an experiment (TABLE 3) Resultant histological studies of certain body tissues would show pathological symptoms with intensities proportional to drug intake The above discussion presents only a few examples of problems arising in chronic toxicity tests, and is intended only to emphasize the need for proper interpretation of data obtained on food consumption in relation to growth

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SHORTCOMINGS OF FOOD CONSUMPTION AS A MEASURE OF HUNGER; RESULTS FROM OTHER BEHAVIORAL TECHNIQUES

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I have been tremendously impressed by the work so effectively reported at the Conference on which this monograph is based It is interesting to note, however, that almost all of the studies referred to have used as their index of hunger a single technique, namely, the amount of food eaten If one is in- [illegible] measure the maximum intensity of the hunger For example, a persistent, or recurring, low level of hunger which keeps the subject nibbling would cause a large consumption of food, while an intense but rapidly satiated hunger would produce a smaller consumption Furthermore, the total consumption probably depends on the balance between *two* factors hunger and the motivation to stop eating

The foregoing type of analysis is supported by a study by Miller, Bailey, and Stevenson[3] on rats with the hypothalamic lesions which cause obesity On *ad lib* feeding tests, these animals ate much *more* food than did normal controls But a series of behavioral tests showed that they worked *less hard* for food and were *more easily* deterred from eating it Therefore, we concluded that, under certain conditions, the hypothalamic animals can react to food deprivation with a less intense hunger, even though they eat more on an *ad lib* diet *

I shall briefly illustrate two of the behavioral measures which we have found [illegible] strength of hunger Furthermore, since the animals get only tiny bits of food infrequently, relatively long tests can be made without appreciably satiating hunger

The other measure involves pitting the aversion produced by quinine against appetite Animals are presented with a series of tiny samples of food, each of

* Under somewhat different conditions, which are not yet well understood by us, the rats with hypothalamic lesions can not only eat more but also work harder for food

which is adulterated by an increasing proportion of quinine As might be expected, the hungrier animals progress farther up the series into the higher [illegible]

A somewhat similar discrepancy between the consummatory and the other two behavioral measures appears in studying the effects of different durations of food deprivation We have compared four techniques under exactly the same conditions The amount of food which the rats ate immediately after various periods of deprivation increased rapidly during the first 6 hours and reached a maximum somewhere in the neighborhood of 30 hours, after which it tended to fall off The total excursion of stomach contractions (recorded from a balloon on the end of a chronically implanted plastic fistula) increased rapidly during the first six hours, after which it tended to level off. But our other two measures, the rate of bar pressing and the amount of quinine required to stop eating, continued to increase with food deprivation throughout the 54 hours measured In some of our other experiments, the rate of bar pressing has continued to *increase* for at least 4 days, while the amount of food consumed has continued to *decrease* after 24 hours Thus, at the higher levels, the amount of food consumed does not seem to be a good measure of hunger It seems to be limited by the volume of the stomach, or the capacity of the organism to deal with the food Furthermore, this limit decreases during more extreme deprivation

Under other circumstances, the consummatory and the performance measures may agree The studies made in our laboratory of the role of oral-pharyngeal factors are good examples * Kohn[2] found that the rate of bar pressing aperiodically reinforced by food was relatively unaffected by an immediately preceding injection of 14 cc of isotonic saline directly into the stomach via a chronic plastic fistula But 14 cc of milk injected directly into the stomach produced a marked reduction in the rate of bar pressing, and the same amount of milk drunk normally by mouth produced an even greater reduction Berkun, Kessen, and Miller[1] secured exactly similar results when the amount of milk drunk was used as a test Furthermore, Miller and Kessen[4] found that milk injected directly into the stomach served as a reward for learning a simple T-maze, but that milk taken normally by mouth served as a stronger reward to produce more rapid learning

As a supplement to the chronic fistula technique, we have used saccharin, a sweet tasting but nonnutritive substance, to test for oral-pharyngeal effects As a control, we have used an equal volume of a saline solution matched for sodium content with the sodium saccharide In one series of experiments, this control solution was administered by mouth. So that they would drink it, the rats were thirsty as well as hungry Tests showed that the saline and saccharin solutions were equally effective in reducing thirst, but differed in their short-range effects on hunger Compared with the control, prefeeding with saccharin solution reduced both the subsequent consumption of that solution and the

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rate of bar pressing reinforced by saccharin It also reduced the immediately succeeding consumption of dextrose, milk, lab chow, or fat The effects of saccharin were less, however, than those of an equally preferred solution of dextrose This reduction seemed to be due to the fact that dextrose had both an oral-pharyngeal and a gastrointestinal effect, while saccharin had only the former In contrast with the results on nutritive substances, saccharin administered via stomach fistula had no effect, only when taken by mouth did it reduce subsequent consumption or performance

In conclusion, I should like to illustrate how yet another behavioral technique has been used to demonstrate a qualitative difference between two otherwise similar effects We have studied the effects of stomach distention by using rats with two plastic fistulas chronically implanted into their stomachs On the end of one of these fistulas was a rubber balloon We compared the effect of injecting milk via fistula into the stomach with that of injecting an equal volume of a saline solution of equal specific gravity into the balloon in the stomach Both procedures reduced the rate at which rats would work at pressing a bar to get food The effects of the milk were slightly, but statistically reliably, greater When studied by this technique, the effects of stomach distention by balloon and by milk were qualitatively similar, and only slightly different quantitatively In other experiments,[5] we used a learning technique Hungry rats were given trials in a simple T-maze If they chose a given side (for example, turned to the right), one group had milk injected via fistula directly into their stomachs, and the other group had an equal volume of saline injected into their stomach balloons The rats whose stomachs were distended by milk learned to *choose* that side, but the rats whose stomachs were distended by the balloon learned to *avoid* that side We conclude that two qualitatively different factors must be involved One of these factors might be a reduction in the strength of the hunger drive, which should be rewarding, and the other might be the induction of some conflicting motivation, such as nausea, which should be punishing In any event, it is clear that the rewarding effects were dominant when the stomach was distended by milk and the punishing ones were dominant when it was distended by the balloon The two treatments produced qualitatively different effects

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